The role of loneliness in the neurocognitive processing of psychosocial stress and trauma

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List of abbreviations

ACC	anterior cingulate cortex
DMN	default mode network
fMRI	functional magnetic resonance imaging
HPA	hypothalamic-pituitary-adrenal
PTSD	post-traumatic stress disorder
RQ	research question
vmPFC	ventromedial prefrontal cortex

1. Abstract

Loneliness is a ubiquitous problem in modern societies due to its detrimental psychological and physiological health effects. Loneliness is closely associated with psychosocial stress, a link further exacerbating mental health problems and subjective suffering. The following thesis tried to shed light on the interconnection between the physiological and psychological phenotypes of stress and loneliness and investigate their consequences for mental well-being. Thus, study 1 examined alexithymia as a predictor for psychosocial stress during social transition phases with an additional focus on how loneliness contributes to this connection. Therefore, alexithymia, loneliness, and perceived stress were monitored in first-year students and functional magnetic resonance imaging (fMRI) was conducted at the beginning and six months after their transition to university. The results demonstrated that alexithymia predicted higher psychosocial stress via enhanced loneliness levels. On a neural level, insula reactivity mediated the connection between alexithymia and loneliness. Study 2 investigated romantic relationships and current living situations as possible protective factors for loneliness and stress during the COVID-19 lockdown. To that end, momentary loneliness and cortisol levels were assessed. The study revealed that romantic relationships and living with others could protect against loneliness, whereas romantic relationships might even reduce neuroendocrine stress response showing the protective quality of social connectedness during challenging times. To elucidate the role of loneliness as a potential risk factor for psychopathology, study 3 applied an experimental trauma paradigm to elicit intrusive thoughts in a sample of lonely and non-lonely subjects. Prior to trauma exposure, an fMRI scan was conducted to examine loneliness-related changes in neural fear processing. Results showed an interaction of sex and loneliness, with high lonely men exhibiting more intrusive thoughts and an amygdala hyperreactivity to fear signals implying increased vulnerability after trauma exposure. Moreover, a literature review (study 4) was conducted as part of this thesis to outline structural and functional neural changes related to loneliness. To summarize, the presented results confirm that loneliness acts directly on the neuroendocrine and neural stress systems, potentially enhancing the malicious effects of stress on psychopathology. Hence, new studies should focus on deepening the understanding of the neural pathways of loneliness to tailor new neuroscientifically informed therapies targeting perceived social isolation.

2. Introduction and research aims

2.1. Evolutionary perspective on loneliness

"Everyone will concede that man is a social being. We see it in his aversion to loneliness as well as his desire for companionship beyond the confines of his family."
Charles Darwin (1871)

As Darwin postulated in his opus magnum "The Descent of Man, and Selection in Relation to Sex", it is unquestionable that humans are a social species and that loneliness is indeed an aversive and unpleasant feeling. Interestingly, nearly 150 years later, Cacioppo and colleagues hypothesized that feelings of loneliness might be an evolutionary signal to increase social bonding, enhancing the individual survivability (Cacioppo et al., 2014). Thus, loneliness might be an adaptive function to promote behavioral changes in the same way hunger triggers the need for food intake (Tomova et al., 2020). Hence, the absence of meaningful social connections over a prolonged period could have detrimental health consequences just as starving has.

Indeed, accumulating evidence indicates that chronic loneliness, defined as the discrepancy between desired and actual social connectedness (Perlman and Peplau, 1981), has harmful effects on mental and even physical health. Loneliness is therefore increasingly recognized as a critical public health issue in rapidly aging and urbanized societies, with prevalence ratings between 5.2% to 9.6% for middle-aged Europeans (Surkalim et al., 2022). Given the recent COVID-19 pandemic with its extended periods of lockdowns and social distancing, loneliness levels might have increased in vulnerable populations, further fostering the urgency to explore the mechanisms of loneliness more thoroughly (Bu et al., 2020; Killgore et al., 2020).

Various lines of research established that loneliness is linked with an increased mortality risk comparable to well-established risk factors such as obesity or smoking (Holt-Lunstad et al., 2010). In addition, loneliness has not only been associated with mental disorders like depression and anxiety disorders but also with physical maladies like coronary heart disease and stroke (Beutel et al., 2017). Besides these negative implications of loneliness, the acute stress response itself seems to be modulated by loneliness. Hence, high levels

of loneliness might predict an exaggerated physiological stress response (Brown et al., 2019). Thus, this thesis aims to deepen the knowledge of the interplay between loneliness and psychosocial stress.

2.2. Loneliness and stress dynamics

Loneliness modifies the acute stress response by enhancing inflammatory and cardiovascular reactivity (Brown et al., 2018). Additionally, detrimental forms of emotion-oriented stress coping are linked to loneliness (Deckx et al., 2018) and feelings of loneliness seem to directly influence the hypothalamic-pituitary-adrenal (HPA) axis demonstrated by heightened cortisol secretion (Adam et al., 2006). Therefore, the feeling of social isolation could increase the allostatic load, defined as the wear and tear resulting from an overactivity of the stress system (McEwen, 1998). It is well known that chronic stress, similar to loneliness, can lead to physiological and psychological problems like cardiovascular diseases and anxiety disorders. Thus, one potential mechanism contributing to the maleficent health effects of loneliness could be an interplay with stress reactivity.

An opportunity to study the relationship between loneliness and stress arises in social transition phases like the progression from school to university or from work to retirement. Life's transition phases are accompanied by increased psychosocial stress and changes in the social environment (Fisher and Hood, 1987). Interestingly, these transition phases correspond to the U-shape distribution of loneliness with high loneliness scores in young and older adults (Solmi et al., 2020). Nevertheless, it is still unclear which mechanisms are involved in the interplay between loneliness and increased psychosocial stress. A possible risk factor for increased psychosocial stress during transition might be alexithymia, characterized by impaired emotional awareness and interpersonal relating. According to the stress-alexithymia hypothesis, high levels of alexithymia lead to ineffective coping, hence increasing the allostatic load (Martin and Pihl, 1985). In addition, alexithymia has been linked to elevated levels of loneliness (Qualter et al., 2009). Thus, it is conceivable that the relationship between alexithymia and heightened psychosocial stress could be influenced by loneliness.

The COVID-19 pandemic as a temporary social transition phase with periods of prolonged social isolation provided the unique opportunity to study protective factors reducing

loneliness and stress in a naturalistic setting. In line with the social buffering hypothesis (Cohen and McKay, 1984), which proposes that healthy relationships could buffer stress-related health consequences, positive social interactions could therefore reduce short-term stress correlates, particularly cortisol levels. For example, affectionate romantic relationships lower loneliness and psychosocial stress levels (Ditzen et al., 2019; Vozikaki et al., 2018) and married individuals even show lower cortisol levels, as well as faster cortisol decline (Chin et al., 2017). Along with relationship status, living alone constitutes a crucial risk factor for being lonely and is increasingly prevalent in western societies (Greenfield and Russel, 2010). Additionally, living with others decreases loneliness levels, whereas cortisol secretion is heightened in individuals living alone, indicating that living with others might also reduce psychosocial stress (Bu et al., 2020; Stafford et al., 2013). Therefore, living in a romantic relationship or with close others could buffer COVID-19 related mental health consequences via decreased levels of loneliness and reduced cortisol secretion.

While COVID-19 offered the chance to study protective factors for loneliness, it also demonstrated the dire need to investigate loneliness as a potential risk factor for psychiatric disorders more thoroughly. Mental health declined during COVID-19 lockdown periods and specifically trauma symptomatology increased due to heightened psychosocial stress levels (Salehi et al., 2021). Moreover, a higher trauma symptom load is associated with not being in a relationship and living alone, possibly linking loneliness and trauma symptomatology (Lahav, 2020). Indeed, loneliness predicts and is itself predicted by post-traumatic stress disorder (PTSD) symptoms, indicating a bidirectional relationship (van der Velden et al., 2018). PTSD is a frequently chronic condition triggered by a traumatic event, with prevalence rates being higher in women than men (Kimerling et al., 2018). Most trauma therapies focus on exposure-based interventions to reduce fear responses, which are mechanistically connected with fear habituation and extinction processes (Norrholm et al., 2011). In addition, fear extinction is impaired by high stress levels (Maren and Holmes, 2016). One main symptom and predictor of PTSD are intrusive thoughts, defined as spontaneous memories depicting the traumatic event, mostly in visual forms of mental imagery. Intrusive thoughts are linked to a neural dysfunction of the amygdala-hippocampus complex (Anderson and Floresco, 2022). Therefore, further exploring the bidirectional relationship of trauma and loneliness and their accompanied

neural changes might be helpful to further detangle the ways loneliness mediates its deleterious effects.

2.3. Neurobiological factors of loneliness

Loneliness has been linked to morphological as well as functional neural changes. A recent study showed that a 14-month-long Antarctica expedition with extended periods of social isolation led to a significant decrease in gray matter volume (Stahn et al., 2019). Even though objective social isolation should not be mistaken with loneliness, loneliness itself is associated with volume changes, for example, in the anterior cingulate cortex (ACC), fusiform gyrus, and dorsolateral prefrontal cortex (Bzdok and Dunbar, 2022). Moreover, loneliness-dependent changes in functional connectivity were observed in the default mode network (DMN) (Spreng et al., 2020).

Interestingly, loneliness affects neural pathways, which have also been linked to alexithymia. A meta-analysis demonstrated that alexithymia is connected with blunted emotional responses in the limbic system, namely the ACC, insular cortex, and amygdala (van der Velde et al., 2013). Additionally, ACC-insula coupling as well as amygdala reactivity are associated with stress resilience (Shao et al., 2018; Yamamoto et al., 2017). Neurofeedback training of the amygdala enhances stress coping and reduces alexithymia (Keynan et al., 2019). Furthermore, these brain regions were also identified to exhibit reduced activity to positive emotional stimuli in high lonely subjects (Cacioppo et al., 2009). These findings indicate that alexithymia, stress, and loneliness are not only connected on a behavioral or neuroendocrine level but indeed share common neural pathways in the limbic system potentially causing detrimental ramifications.

In the same way, loneliness is neuronally linked with alexithymia through the limbic system, the amygdala might play a crucial role in mechanistically connecting loneliness and trauma. Studies showed that lonely subjects exhibit smaller amygdala grey matter volume (Düzel et al., 2019). Additionally, amygdala volume moderates loneliness levels after an physical exercise intervention via decreased stress levels (Ehlers et al., 2017). Furthermore, loneliness is associated with volume changes in the amygdala and ventromedial prefrontal cortex (vmPFC) in a sex-dependent matter, with lonely men showing smaller amygdala and higher vmPFC volumes in contrast to lonely women (Kiesow et al., 2020).

Looking at the amygdala's role in trauma processing, former studies demonstrated that increased amygdala response during trauma exposure predicts intrusive thought formation (Rattel et al., 2019a). Furthermore, women exhibit sustained amygdala responses to familiar negative cues which could relate to increased intrusions and slowed extinction learning after trauma exposure (Andreano et al., 2014; Rattel et al., 2019b). Interestingly, both fear extinction and habituation, basis of most modern trauma therapies, recruit a network including the amygdala (Furlong et al., 2016). Moreover, trauma disclosure has been related to reduced intrusions and altered functional connectivity of the amygdala (Scheele et al., 2019). The opportunity for trauma disclosure might be reduced in individuals with a lack of meaningful social contacts and high levels of loneliness. Given the involvement of the amygdala in both loneliness and trauma, it is plausible that loneliness might influence trauma and neural fear processing directly via an amygdala pathway.

2.4. Research aims

This thesis aims to investigate the influence of loneliness on stress dynamics and psychopathology. Thus, three studies were conducted to study the influence of loneliness on the interplay between alexithymia and stress (study 1), to identify protective social factors for psychosocial stress during the COVID-19 pandemic (study 2), and to investigate loneliness as a potential risk factor for trauma-related intrusions (study 3). The following research questions (RQ) were addressed in this thesis:

RQ 1: Does loneliness influence the interplay between psychosocial stress and alexithymic traits during social transition phases?

RQ 2: Do relationship status and living situation act as protective factors by reducing loneliness and cortisol levels during the COVID-19 lockdown?

RQ 3: Do lonely subjects exhibit more intrusive thoughts after trauma exposure in a sex-dependent manner and is this phenotype related to amygdala activity before trauma exposure?

All studies tried to shed light on the intertwined phenotypes of loneliness and psychosocial stress on an endocrine or neural level. The results of the current studies might help to

evolve new interventions to reduce loneliness and improve mental health. In addition, to summarize these findings and discuss the neurocognitive mechanisms of chronic loneliness, an additional review paper was written to complement this thesis (study 4).

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3. Publications

Publication overview:

Morr M, Lieberz J, Dobbelstein M, Philipsen A, Hurlemann R, Scheele D. Insula reactivity mediates subjective isolation stress in alexithymia. Sci Rep 2021; 11(1): 15326 [IF: 4.99]

Hopf D, Schneider E, Aguilar-Raab C, Scheele D, **Morr M**, Klein T, Ditzen B, Eckstein M. Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality. Sci Rep 2022; 12(1): 15076 [IF: 4.99]

Morr M, Noell J, Sassin D, Daniels J, Philipsen A, Becker B, Stoffel-Wagner B, Hurlemann R, Scheele D. Lonely in the Dark: Trauma Memory and Sex-Specific Dysregulation of Amygdala reactivity to Fear Signals. Adv Sci 2022; 9(15): 2105336 [IF: 17.52]

Morr M, Liu X, Hurlemann R, Becker B, Scheele D. Chronic loneliness: neurocognitive mechanisms and interventions. Psychother Psychosom 2022; 91(4): 227-237 [IF: 25.61]

3.1. Publication 1: Insula reactivity mediates subjective isolation stress in alexithymia

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Insula reactivity mediates subjective isolation stress in alexithymia

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The risk for developing stress-related disorders is elevated in individuals with high alexithymia, a personality trait characterized by impaired emotional awareness and interpersonal relating. However, it is still unclear how alexithymia alters perceived psychosocial stress and which neurobiological substrates are mechanistically involved. To address this question, we examined freshmen during transition to university, given that this period entails psychosocial stress and frequently initiates psychopathology. Specifically, we used a functional magnetic resonance imaging emotional face matching task to probe emotional processing in 54 participants (39 women) at the beginning of the first year at university and 6 months later. Furthermore, we assessed alexithymia and monitored perceived psychosocial stress and loneliness via questionnaires for six consecutive months. Perceived psychosocial stress significantly increased over time and initial alexithymia predicted subjective stress experiences via enhanced loneliness. On the neural level, alexithymia was associated with lowered amygdala responses to emotional faces, while loneliness correlated with diminished reactivity in the anterior insular and anterior cingulate cortex. Furthermore, insula activity mediated the association between alexithymia and loneliness that predicted perceived psychosocial stress. Our findings are consistent with the notion that alexithymia exacerbates subjective stress via blunted insula reactivity and increased perception of social isolation.

Major life events such as the transition from school to university or from work to retirement involve changes in the social environment and are frequently accompanied by increased psychosocial stress[1]. The allostatic load[2], that is the wear and tear resulting from chronic overactivity of stress systems, can increase the risk of stress-related disorders like major depression or anxiety. Both environmental factors and interindividual differences modulate the allostatic load. Specifically, the ability to effectively cope with a life stressor is decreased in individuals with high alexithymia[3], a personality trait characterized by impaired emotional awareness and interpersonal relating. According to the stress-alexithymia hypothesis[4], the lack of emotional awareness hinders the identification of an event as stressful and the resulting ineffective coping aggravates the allostatic load. In fact, there is accumulating evidence that alexithymia has detrimental effects on mental and physical health[5–7]. In addition, alexithymia is associated with dysfunctional interpersonal bonding, which might lead to distressful feelings of loneliness if the quality or quantity of social relationships does not satisfy a person's need to belong[8,9]. Loneliness and social withdrawal in turn foster depressive symptomatology[10] and may increase the risk of relapse[11]. Furthermore, recent studies support close associations between loneliness, atypical physiological responses to acute stress and detrimental emotion-oriented stress coping strategies[12–15]. Collectively, not only the objective availability of support via social networks may modulate the allostatic load during transition phases, but also the subjective perception of social connectedness. Therefore, alexithymia might negatively impact psychological well-being and mental health via impaired interpersonal relating[16,17]. However, while the stress-alexithymia hypothesis is well established, it is still unclear whether alexithymia affects perceived stress during social transition phases by enhancing feelings of loneliness. Moreover, little is known about the underlying neurobiological mechanisms that promote the detrimental effects of alexithymia on stress responses.

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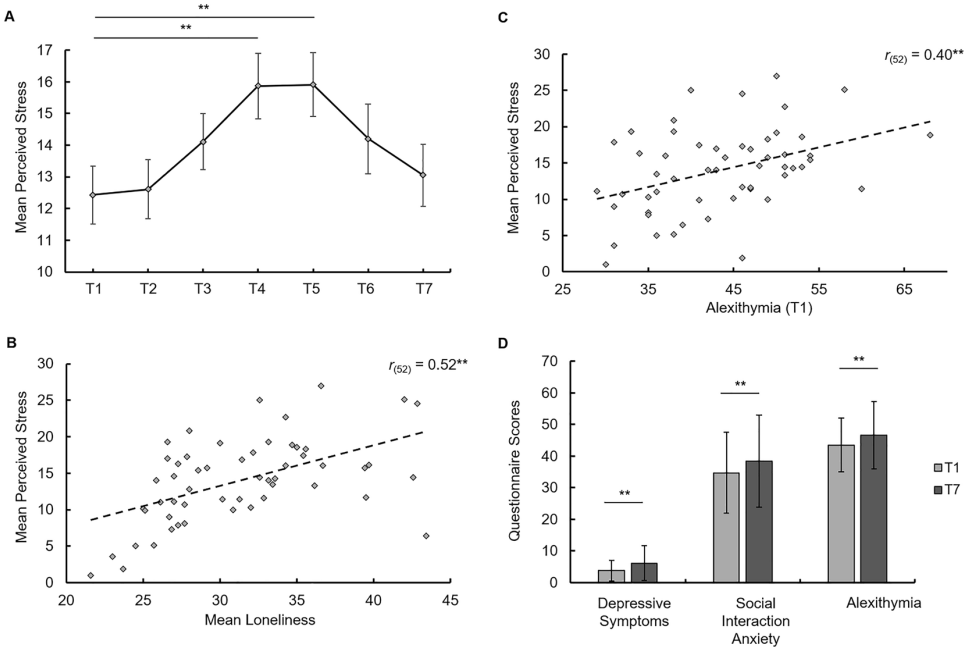

Figure 1. Perceived stress significantly changed over time and peaked in months four and five of the observation period (**A**). Mean perceived stress positively correlated with mean loneliness (**B**) and alexithymia (**C**) at study entry. Depressive symptoms, social interaction anxiety and alexithymia significantly increased after 6 months (**D**). Error bars show the standard error of the mean. $^{**}p < 0.01$, T1–T7, first to seventh month.

Importantly, alexithymia and loneliness seem to affect similar neural pathways: a meta-analysis of neuroimaging studies[18] revealed that high levels of alexithymia are associated with blunted responses to emotional stimuli (e.g. happy and fearful faces) in a limbic neurocircuitry including the amygdala and insular cortex and elevated responses in the anterior cingulate cortex (ACC) that may reflect difficulties in identifying and regulating emotions. Likewise, in highly lonely individuals, pleasant social stimuli elicited less activity in the striatum, amygdala, insula and ACC[19]. Of note, these brain regions have been identified as important neural hubs of stress resilience such that robust amygdala responses to emotional stimuli and functional coupling of ACC-insula circuitry might promote adaptive stress responses[20,21]. Moreover, a recent study demonstrated that targeted amygdala neurofeedback improves stress coping and reduces alexithymia[22], further strengthening the assumption that alexithymia and loneliness prevent favorable stress response by shared neural response patterns.

The current study thus aims to probe whether alexithymia might affect perceived stress by enhancing feelings of loneliness and to examine which neural substrates are involved. Therefore, we measured alexithymic traits and neural activation patterns in response to social stimuli (emotional faces) during functional magnetic resonance imaging (fMRI) in a sample consisting of 54 healthy freshmen. Participants were monitored during their first 6 months of the transition to university. Each month, participants completed questionnaires measuring their loneliness and their subjective stress experiences during this major life event. Specifically, we hypothesized a positive correlation between alexithymia and subjective stress response across time and that this relationship would be mediated by feelings of loneliness. Given the intertwined phenotype of alexithymia and loneliness as well as the overlapping neural correlates of both constructs, we predicted that both higher alexithymic traits and higher loneliness levels would be associated with altered responses to emotional face stimuli in the ACC, insula and amygdala. To this end, we used alexithymia and loneliness scores as continuous covariates in the analyses. Finally, we expected that the link between alexithymia and perceived stress would be mechanistically mediated by altered activity in these brain regions.

Results

Behavioral results. Stress levels changed significantly over time ($F_{(6,294)} = 4.56$, $p < 0.01$, $\eta_p^2 = 0.09$) and peaked in month four ($t_{(52)} = 4.48$, Bonferroni-corrected p (p_{cor}) < 0.01, $d = 0.47$) and five ($t_{(53)} = 3.92$, $p_{cor} = 0.02$, $d = 0.49$) of the observation period in comparison to the stress levels at study entry (see Fig. 1A), reflecting the first examination phase. In contrast, social network size ($F_{(6,282)} = 0.96$, $p = 0.43$, $\eta_p^2 = 0.02$) and loneliness scores ($F_{(6,288)} = 1.69$, $p = 0.14$, $\eta_p^2 = 0.03$) did not significantly change during the time course (see Table S1). As predicted, both the average loneliness ($r_{(52)} = 0.52$, $p < 0.01$; see Fig. 1B) and alexithymia in the first month (T1) positively correlated with the average perceived stress in the 6 months ($r_{(52)} = 0.40$, $p < 0.01$; see Fig. 1C), showing that individuals with greater dysfunctional emotional awareness and higher subjective lack of social con-

nection experienced more stress during the transition phase. In addition, T1 alexithymia positively correlated with psychosocial stress ($r_{(52)} = 0.49$, $p < 0.01$) already at study entry, but was not significantly associated with the increase in stress levels (i.e. maximum stress minus baseline) during the first examination phase ($p > 0.05$), indicating that alexithymia is associated with consistently increased perceived stress levels rather than increased acute stress responsiveness. Furthermore, depressive symptoms ($t_{(53)} = 3.19$, $p < 0.01$, $d = 0.53$), social interaction anxiety ($t_{(53)} = 3.05$ $p < 0.01$ $d = 0.26$) and alexithymia ($t_{(53)} = 2.83$, $p < 0.01$, $d = 0.32$) significantly increased after 6 months (see Fig. 1D).

fMRI task effects. Across both fMRI sessions, the participants exhibited increased responses to emotional faces (fearful and happy) compared to neutral ones in middle temporal regions (L (left): x, y, z coordinates of peak voxel in Montreal Neurological Institute space (MNI_{xyz}): − 60, − 56, 2, $k_E = 125$, after familywise error corrections (p_{FWE}) on cluster level $p_{FWE} = 0.02$; R (right): MNI_{xyz}: 58, − 58, 12, $k_E = 198$, $p_{FWE} < 0.01$), the inferior temporal gyrus (MNI_{xyz}: − 42, − 42, − 16, $k_E = 135$, $p_{FWE} = 0.01$) and middle occipital regions (L: MNI_{xyz}: − 22, − 98, 0, $k_E = 723$, $p_{FWE} < 0.01$; R: MNI_{xyz}: 26, − 90, 0, $k_E = 925$, $p_{FWE} < 0.01$). Furthermore, subjects showed stronger activation in response to fearful faces relative to neutral faces in clusters including the middle temporal gyrus (L: MNI_{xyz}: − 58, − 52, 4, $k_E = 293$, $p_{FWE} < 0.01$; R: MNI_{xyz}: 58, − 58, 14, $k_E = 533$, $p_{FWE} < 0.01$), the left inferior temporal gyrus (MNI_{xyz}: − 42, − 44, − 16, $k_E = 206$, $p_{FWE} < 0.01$), the right occipital region (MNI_{xyz}: 26, − 90, 0, $k_E = 589$, $p_{FWE} < 0.01$) and lingual areas in the left hemisphere (MNI_{xyz}: − 20, − 90, − 14, $k_E = 591$, $p_{FWE} < 0.01$). Moreover, subjects showed increased activity in middle occipital regions (L: MNI_{xyz}: − 20, − 98, 2, $k_E = 437$, $p_{FWE} < 0.01$; R: MNI_{xyz}: 32, − 92, 6, $k_E = 537$, $p_{FWE} < 0.01$) in response to happy faces compared to neutral ones. There were no significant whole-brain differences between the first (T1) and the seventh month (T7).

Correlation analyses of alexithymia and loneliness with brain activation. Individuals with high alexithymia showed decreased right amygdala responses to emotional faces in contrast to neutral faces at T1 (MNI_{xyz}: 34, 2, − 24, $t_{(53)} = 3.55$, $p_{FWE} = 0.03$ on peak level; see Fig. 2A). Furthermore, subjects with higher loneliness exhibited reduced activation in response to emotional faces in the left and right anterior insula (L: MNI_{xyz}: − 36, 12, 8, $t_{(53)} = 4.36$, $p_{FWE} = 0.02$; R: MNI_{xyz}: 48, 8, 4, $t_{(53)} = 4.21$, $p_{FWE} = 0.03$; see Fig. 2B), and ACC (L: MNI_{xyz}: 0, 28, 24, $t_{(53)} = 4.85$, $p_{FWE} < 0.01$; R: MNI_{xyz}: 2, 26, 24, $t_{(53)} = 4.82$, $p_{FWE} < 0.01$; see Fig. 2C) at T1. Likewise, loneliness negatively correlated with responses to fearful faces in the left anterior insular cortex (MNI_{xyz}: − 34, 10, 10, $t_{(53)} = 4.73$, $p_{FWE} = 0.01$) and ACC (L: MNI_{xyz}: 0, 8, 26, $t_{(53)} = 4.79$, $p_{FWE} = 0.01$; MNI_{xyz}: 0, 28, 24, $t_{(53)} = 4.70$, $p_{FWE} = 0.01$; R: MNI_{xyz}: 2, 26, 24, $t_{(53)} = 4.52$, $p_{FWE} = 0.01$; MNI_{xyz}: 2, 8, 28, $t_{(53)} = 4.03$, $p_{FWE} = 0.03$) and anterior insula responses (MNI_{xyz}: 34, 12, 4, $t_{(53)} = 4.12$, $p_{FWE} = 0.04$) to happy faces. These associations were not evident at T7.

Mediation analysis. To examine whether higher levels of alexithymia predicted perceived stress levels by enhancing feelings of loneliness, a first mediation analysis was calculated with alexithymia as predictor for subjective stress and loneliness as mediator. A significant mediation via loneliness [indirect effect of alexithymia on stress via loneliness: β = 0.20, standard error (SE) = 0.10, 95% confidence interval (CI) 0.04–0.43] indicated that the detrimental effects of alexithymia on perceived stress were indeed mediated by loneliness with the direct effect of alexithymia on stress being diminished after including loneliness (total effect of alexithymia on stress: β = 0.40, $p = 0.003$, SE = 0.13, 95% CI 0.15–0.66; direct effect of alexithymia on stress after including loneliness as mediator: β = 0.20, $p = 0.14$, SE = 0.13, 95% CI −0.07 to 0.47). In a second step, we added the parameter estimates of the right amygdala, right ACC and right anterior insula as further mediator variables to the model to elucidate the underlying neural mechanisms. For each brain region, two models were calculated to test potential mediation effects on all pathways (i.e., both serial and parallel mediation effects were tested). The analyses revealed that the link between alexithymia and loneliness was driven by reduced insula reactivity, leading to a significant indirect effect of alexithymia on stress via insula reactivity and loneliness (serial mediation: β = 0.06, SE = 0.04, 95% CI 0.01–0.15, see Fig. 3). Specifically, alexithymia predicted the reduced anterior insula reactivity which was linked to enhanced feelings of loneliness which in turn, predicted subjective stress. This mediation was mainly driven by the Toronto Alexithymia Scale (TAS) factors "difficulties describing feelings" (DDF) and "difficulties identifying feelings" (DIF) (see SI Results). No further mediation effects were observed for the insula, amygdala or ACC (all 95% CIs of further indirect effects via brain activation included zero).

Discussion

The present study aimed at elucidating the neural mechanisms moderating the link between alexithymic traits, loneliness and stress reactivity during the transition to university. Our results confirmed that loneliness mediated the noxious association between alexithymia and subjective stress during the first 6 months of university. Moreover, we found that the anterior insula plays a crucial role in this process, by mediating the link between alexithymia and loneliness.

Our results provide further support for and extend the stress-alexithymia hypothesis[4]. We were able to replicate previous models suggesting a close link between alexithymia and loneliness[11] and found that individuals with high alexithymia, especially with difficulties in describing and identifying emotions, experience more stress during transition phases partly because they perceive more subjective social isolation. This finding is consistent with previous studies reporting significant associations between the TAS DIF and DDF subscales and loneliness[23] as well as a relationship between the TAS DIF subscale and poor adjustment during transition to university and perceived stress[24]. Intriguingly, our results indicate that this mechanism may be driven by diminished insula responses to emotional signals which directly link alexithymia with loneliness. The insular cortex is a hub for interoceptive processing and conscious affect[25] and endotoxin-induced changes in the glucose metabolism of

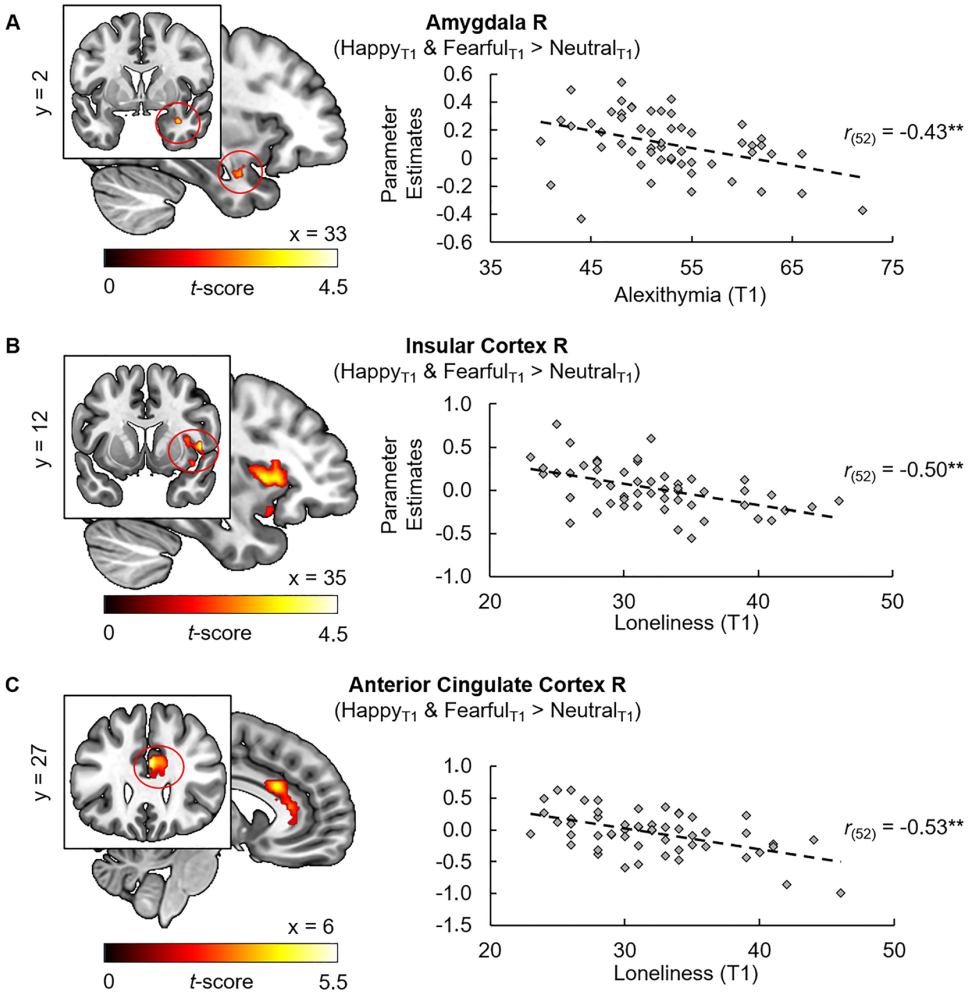

Figure 2. Participants with high alexithymia showed reduced activation to emotional faces compared to neural faces in the right amygdala (**A**; MNI_{xyz}: 34, 2, − 24, $t_{(53)} = 3.55$, $p_{FWE} = 0.03$). Individuals with high loneliness exhibited lower responses to emotional faces in the right anterior insular cortex (**B**; MNI_{xyz}: 48, 8, 4, $t_{(53)} = 4.21$, $p_{FWE} = 0.03$) and the right anterior cingulate cortex (**C**; MNI_{xyz}: 2, 26, 24, $t_{(53)} = 4.82$, $p_{FWE} < 0.01$). For illustration purpose clusters are shown with significance level of $p = 0.05$. $^{**}p < 0.01$, *FWE* familywise error corrected, *L* left, *MNI* Montreal Neurological Institute, *R* right, *T1* study entry.

the right insula positively correlate with changes in social interest[26]. Likewise, individuals with high loneliness have been found to exhibit reduced insula responses during interpersonal trust decisions[27]. Moreover, multiple lines of evidence indicate that insula pathology leads to alexithymia. For instance, dopamine D2-type receptor availability in the insula has been linked to higher alexithymia[28], the gray matter volume of the insular cortex inversely correlated with alexithymia[29] and the extent of damage to the anterior insula predicted alexithymia in lesion patients[30]. It has been theorized that insula dysfunction in alexithymia may reflect a transdiagnostic marker of empathic deficits[31] and our findings in healthy participants point to an additional mechanism such that the dampened insula responses to external emotional cues underlie the association of alexithymia with enhanced perceived social isolation. Along these lines, the observed pattern of results is consistent with the notion that social connectedness requires the ability to flexibly shift between interoceptive and exteroceptive attention[32] which may be based on recruitment of the anterior insula.

Furthermore, consistent with previous fMRI studies[18,19], we found decreased amygdala and ACC responses in individuals with high alexithymia and loneliness, respectively. The amygdala has often been linked to alexithymia[18,33] and a recent study showed that neurofeedback targeting the amygdala during military training not only enhanced stress coping but also decreased alexithymia[22]. Moreover, the amygdala has also been linked to loneliness and social support. For example, a decrease in perceived stress and loneliness was moderated by amygdala volumes[34] and the experience of social support was regulated by amygdala activity[35]. Likewise, the ACC

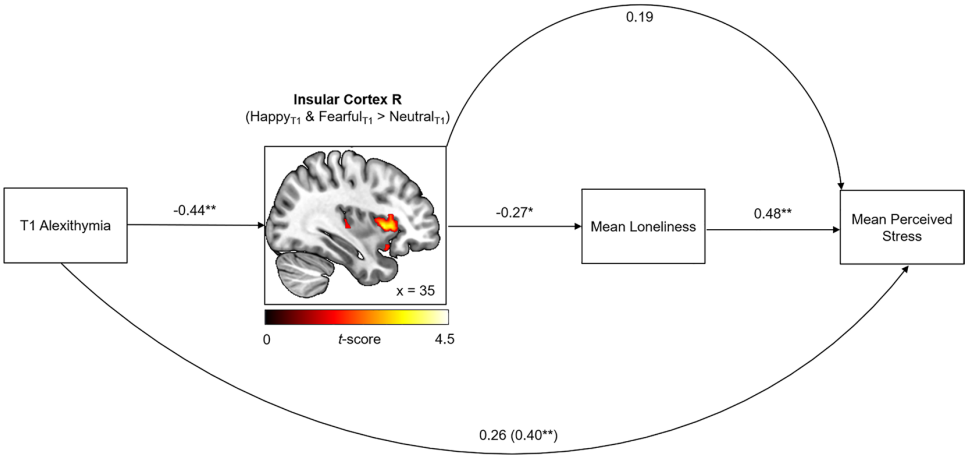

Figure 3. Mean loneliness mediated the relationship between alexithymia at study entry and mean perceived stress ratings. Furthermore, activation of the right insula in response to emotional stimuli at study entry mediated the link between alexithymia and loneliness. Numbers show standardized β coefficients. The β coefficient in brackets shows the total effect without mediators. Insula coordinates are shown in Montreal Neurological Institute space. For illustration purpose, the cluster is shown with a significance level of $p = 0.05$. $^{*}p < 0.05$, $^{**}p < 0.01$, *T1* study entry, *R* right.

has been previously linked not only to loneliness but also to alexithymia: ACC size correlates with alexithymia ratings especially in men[36] and high levels of alexithymia are associated with elevated responses to emotional stimuli in the ACC[18]. Furthermore, the ACC plays a role in social pain processing during social support[37] and overall seems to be a hub for the integration of social information and empathy[38]. Bearing in mind that neither ACC nor amygdala reactivity mediated effects of alexithymia, the insular cortex seems to be a crucial neural processing hub for the interplay between loneliness and alexithymia. Therefore, neurofeedback training targeting insula activation could lead not only to reduced feelings of loneliness but also to reduced psychosocial stress[22]. In contrast to loneliness, objective social network indices were not significantly associated with alexithymia or perceived stress. Given that in a previous study with college freshmen[39] psychological stress selectively mediated the association between antibody response to the influenza immunization and loneliness, but not social network size and immunization response, our data provide further support for the notion that the subjective perception of social connectedness may be a more important predictor for stress reactivity during transition phases than the objectively available social contacts.

Interestingly, the trait-dependent reactivity was no longer evident in the second fMRI session 6 months later, indicating either repetition effects and reduced retest-reliability or that a disrupted plasticity as observed in the prefrontal cortex with an attention-shifting task following long-term psychosocial stress[40] is more pronounced for limbic reactivity to emotional stimuli. Furthermore, we observed an increase in alexithymia scores, potentially elicited by the prolonged subjective stress, which might reflect an acquired secondary alexithymia[41]. As such, these experience-based changes may have masked genuine trait associations in the second fMRI session. Of note, the allostatic load of the transition to university caused a significant increase in depressive symptoms, social interaction anxiety and autistic-like traits after 6 months, thus illustrating that individuals with high alexithymia and loneliness might be at risk not only for poor academic performance but also stress-related psychological disorders due to chronically increased stress levels.

Collectively, our results provide evidence for a close interplay between emotional awareness and perceived social isolation, with dampened insula reactivity serving as a potential underlying mechanism linking alexithymia with loneliness and thus exacerbating the susceptibility to perceived stress. Based on these findings, neurobiologically-informed interventions with cognitive bias modification procedures should target the feeling of social disconnectedness to help students with alexithymic traits to better cope with psychosocial stress during transition phases. Furthermore, neurofeedback training targeting the insula might reduce the feeling of social isolation and therefore potentially enhance stress coping during stressful life events.

Methods

Subjects. Sixty healthy freshman students participated in the study after giving written informed consent. The study was approved by the institutional review board of the medical faculty of the University of Bonn and carried out in compliance with the latest revision of the Declaration of Helsinki. Subjects were screened prior to the first test session and received monetary compensation for study participation. Subjects had no past or present physical or psychiatric illness, as assessed by a medical history questionnaire and the Mini-International Neuropsychiatric Interview[42]. All subjects started their first semester without ever attending university courses before. Six subjects had to be excluded because they missed the second fMRI appointment (n = 3), showed excessive head motion in the MRI (> 3 mm/°; n = 2) or because of technical failures (n = 1). Therefore, final analyses

include data from 54 healthy freshman (39 women, mean age: 18.85 ± 0.88 years minimum [min]/maximum [max] age: 18/22; alexithymia: 45.06 ± 8.79, min/max: 25/68; loneliness: 31.30 ± 5.44, min/max: 20/54). Four subjects missed one of their monthly appointments resulting in data loss of 1.48%.

Experimental design. Subjects were monitored during their first semester at university for a total duration of 6 months, starting with a screening session in their first university month. Shortly (average: 14 days, min/max = 0/32 days) after the screening session, a first fMRI session was conducted (T1 = first month). The fMRI measurements were repeated after 6 months (T7 = seventh month; time between the two fMRI measurements = 164 days, min/max = 153/197 days). Participants completed several questionnaires every month between the two fMRI sessions measuring perceived stress, loneliness and social network size (see Fig. S1).

Questionnaires. Subjects completed different sets of questionnaires to continuously monitor social behavior during their first semester. In the screening session and before the second fMRI scan, we assessed alexithymia (TAS [Toronto Alexithymia Scale][43]), loneliness (UCLA LS [UCLA Loneliness Scale][44]) and perceived stress (PSS-10 [Perceived Stress Scale][45]). Furthermore, we monitored psychiatric symptoms during the transition phase by measuring social interaction anxiety (SIAS [Social Interaction Anxiety Scale][46]), social anxiety (LSAS [Liebowitz Social Anxiety Scale][47]), general trust (GTS [Yamagishi General Trust Scale][48]), autistic-like traits (AQ [Autism Spectrum Quotient][49]), depression symptoms (BDI [Becks Depression Inventory][50]) and trait anxiety (STAI [State Trait Anxiety Inventory][51]). Moreover, to differentiate between subjectively perceived social isolation (i.e. loneliness) and objective social network indices, we included the Social Network Size Questionnaire (SNS)[52]. We further assessed social support (F-SozU [Fragebogen zur Sozialen Unterstützung, short version K-14][53]) as a key resilience factor during transition phases, to further distinguish between perceived social isolation and perceived social support. Every month between these sessions, subjects completed the PSS-10, UCLA LS and SNS. For a detailed description of the TAS, UCLA LS and PSS-10, see SI Methods.

fMRI data acquisition. At the start of the experiment, subjects were instructed to lay as calm as possible. Functional data were acquired with a 3 T Siemens TRIO MRI system (Siemens AG, Erlangen, Germany) with a Siemens 32-channel head coil and obtained by using a T2*-weighted echoplanar (EPI) sequence [TR = 2690 ms, echo time (TE) = 30 ms, ascending slicing, matrix size: 96 × 96, voxel size: 2 × 2 × 3 mm^3, slice thickness = 3.0 mm, distance factor = 10%, field of view (FoV) = 192 mm, flip angle 90°, 41 axial slices]. High-resolution T1-weighted structural images were collected on the same scanner (TR = 1660 ms, TE = 2.54 ms, matrix size: 256 × 256, voxel size: 0.8 × 0.8 × 0.8 mm^3, slice thickness = 0.8 mm, FoV = 256 mm, flip angle = 9°, 208 sagittal slices). To control for inhomogeneity of the magnetic field, fieldmaps were obtained for each T2*-weighted EPI sequence [TR = 392 ms, TE (1) = 4.92, TE (2) = 7.38, matrix size: 64 × 64, voxel size: 3 × 3 × 3 mm^3, slice thickness = 3.0 mm, distance factor = 10%, FoV = 192 mm, flip angle 60°, 37 axial slices].

fMRI task. During the fMRI, subjects completed a well-established emotional face-matching paradigm[54,55]. To ensure the subjects' attention, subjects had to match the identity of two simultaneously presented pictures at the bottom of the screen with a target picture presented at the top. Stimuli consisted of face pictures (neutral, fearful and happy) and houses as non-social control stimuli. Stimuli were presented with Presentation 14 software (Neurobehavioral Systems, Albany, CA, USA) in three blocks for every condition (Happy, Fearful, Neutral, House) with each block consisting of five trials. Stimuli did not vary in emotional expression or in sociality during a block. Trial duration was 5 s with a 10 s pause after each block. In this pause, a fixation-cross was depicted. The identity of the face stimuli varied between T1 and T7 to reduce habituation effects. Participants could choose their responses using an MRI-compatible response grip system (NordicNeuroLab AS, Bergen, Norway). Responses and reaction times (RTs) were measured to evaluate possible attention effects. High-resolution anatomical images were acquired after the functional images.

fMRI analysis. The fMRI data were pre-processed and analyzed using standard procedures in SPM12 (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (The MathWorks Inc., Natick, MA). Participants with excessive head movements (> 3 mm/° in any direction, n = 2) or missing data due to technical failures (n = 1) were excluded from fMRI analyses. The first five volumes of each functional time series were discarded to allow for T1 equilibration. Functional images were corrected for head movements between scans by an affine registration. Images were initially realigned to the first image of the time series before being re-realigned to the mean of all images. To correct for signal distortion based on B0-field inhomogeneity, the images were unwarped by applying the voxel displacement map (VDM file) to the EPI time series (Realign & Unwarp). Normalization parameters were determined by segmentation and non-linear warping of the structural scan to reference tissue probability maps in MNI space. Normalization parameters were then applied to all functional images, which were resampled at 2 × 2 × 2 mm^3 voxel size. For spatial smoothing, a 6-mm full width at half maximum Gaussian kernel was used. Raw time series were detrended using a high-pass filter (cut-off period 128 s).

A two-stage approach based on the general linear model implemented in SPM12 implemented in Matlab (The MathWorks Inc., Natick, MA, USA) was used for statistical analyses. On the first level, participants' individual data were modelled using a fixed-effect model. Onsets and durations of the four experimental condition blocks ('Happy, 'Fearful', 'Neutral', 'House') were modelled by a boxcar function convolved with a hemodynamic response function (HRF). Movement parameters were included in the design matrix as confounds. On the second-level, main contrasts of interest [Fearful $_{First}$ > Neutral $_{First}$; Happy $_{First}$ > Neutral $_{First}$; Fearful $_{Second}$ > Neutral $_{Second}$; Happy $_{Second}$ > Neutral $_{Second}$; Happy $_{First}$ and Fearful $_{First}$ > Neutral $_{First}$; Happy $_{Second}$ and Fearful $_{Second}$ > Neutral $_{Second}$; Happy

$_{\text{First > Second}}$ and Fearful $_{\text{First > Second}}$ > Neutral $_{\text{First > Second}}$; Happy $_{\text{First & Second}}$ and Fearful $_{\text{First & Second}}$ > Neutral $_{\text{First & Second}}$] were computed using one sample t-tests. Loneliness and alexithymia ratings were used as covariates for the second level analysis. The following whole-brain analysis was done with a height threshold of $p < 0.001$. The main analyses of fMRI data focused on regions of interests (ROIs) associated with emotion processing in alexithymia and loneliness consisting of the amygdala, ACC and insular cortex[18]. These ROIs were anatomically defined according to the Wake Forest University PickAtlas (wfu PickAtlas) for both hemispheres. Parameter estimates of significant ROI clusters were extracted using MarsBaR (http://marsbar.sourceforge.net) and further analyzed in SPSS 25 (IBM Corp., Armonk, NY, USA).

Statistical analyses. Repeated measures analyses of variance (ANOVAs) and Bonferroni corrected post-hoc *t*-tests were calculated using SPSS 25 (IBM Corp., Armonk, NY, USA) to examine changes in stress, loneliness and social network size over time. If the assumption of sphericity was significantly violated as assessed by Mauchly's tests, Greenhouse Geisser corrections were applied. Pearson correlations between parameter estimates of significant ROI clusters, loneliness, perceived stress and alexithymia were calculated. Furthermore, mediation analyses were carried out using the PROCESS macro v3.4 for SPSS[56]. Focusing on mean stress as outcome variable, we used T1 alexithymia as predictor variable and mean loneliness ratings as mediator. As we were interested in the neurobiological mechanisms underlying the link between alexithymia, loneliness and perceived stress, we also tested the hypothesized mediation effects of the neural correlates of alexithymia and loneliness. Parameter estimates of significant clusters associated with alexithymia or loneliness at the first fMRI session were thus included as additional mediator variables and mediation effects were tested for each pathway between the former mentioned behavioral results. For all mediation analyses, 10,000 bootstraps samples were used.

Data availability

The data that support the findings of the present study are openly available in the repository of the Open Science Foundation at https://osf.io/csn5u/?view_only=21e52c0df9e14712894596967c4511bc.

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Author contributions

M.M., J.L. and D.S. designed the experiment; M.M., J.L. and M.D. conducted the experiments; M.M., J.L., M.D. and D.S. analyzed the data. All authors wrote the manuscript. All authors read and approved the manuscript in its current version.

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3.2. Publication 2: Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality

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Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality

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Loneliness and social isolation have become increasing concerns during COVID-19 lockdown through neuroendocrine stress-reactions, physical and mental health problems. We investigated living situation, relationship status and quality as potential moderators for trait and state loneliness and salivary cortisol levels (hormonal stress-responses) in healthy adults during the first lockdown in Germany. *N* = 1242 participants (mean age = 36.32, 78% female) filled out an online questionnaire on demographics, trait loneliness and relationship quality. Next, *N* = 247 (mean age = 32.6, 70% female) completed ecological momentary assessment (EMA), collecting twelve saliva samples on 2 days and simultaneously reporting their momentary loneliness levels. Divorced/widowed showed highest trait loneliness, followed by singles and partnerships. The latter displayed lower momentary loneliness and cortisol levels compared to singles. Relationship satisfaction significantly reduced loneliness levels in participants with a partner and those who were living apart from their partner reported loneliness levels similar to singles living alone. Living alone was associated with higher loneliness levels. Hierarchical linear models revealed a significant cross-level interaction between relationship status and momentary loneliness in predicting cortisol. The results imply that widowhood, being single, living alone and low relationship quality represent risk factors for loneliness and having a partner buffers neuroendocrine stress responses during lockdown.

The recent Corona virus (COVID-19) pandemic has been occupying mental and physical health facilities for 2 years now. Hard lockdown regulations in almost all countries early during the pandemic (April until June 2020) to prevent further spreading of the virus entail increased social isolation. The steady and massive health threat from the virus in combination with the missing social buffering effect of everyday social encounters lead to or amplified psychosocial problems that could have long-term consequences for mental and physical health[1–4]. E.g., loneliness, as the subjective and emotional component of social exclusion, is a highly topical and public health issue in modern societies, where social isolation and anonymity become increasingly prevalent[5,6]. It has been previously defined as a psychological aversive state that entails a perceived lack of intimacy or social companionship and the subjective feeling that social relationships are deficient in either quality or quantity[7], which forms the basis of recent research on the topic[8]. By contrast, social isolation is defined as the objective state of being alone[7,9]. According to the belongingness-hypothesis, loneliness is rooted in the human need to socially belong, or the pervasive drive to form and maintain lasting positive and significant social relationships[10]. It has been shown that the sense of belonging in early adolescents is mainly achieved through the acceptance by peers, whereas in late adolescence and adulthood, it is achieved especially by romantic relationships, marital status

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and close friends[11]. On the other hand, lacking feelings of belonging are assumed to be associated with loneliness and negative physical and mental health outcomes in a long-term[10]. Both loneliness and social isolation are significantly related to indices of physical and mental health, such as psychosocial stress[12], depression[13], generalized anxiety[6], cardiovascular diseases[14], chronic obstructive pulmonary disease[15], and mortality[8,9,16–19]. Chronic loneliness may hamper the formation of new social relationships by inducing negative cognitive biases such as interpersonal distrust[20]. Furthermore, loneliness is associated with neuroendocrine parameters, like elevated cortisol levels[21–23] and altered cortisol awakening responses[23,24]. As one of the main effector hormones of the hypothalamus–pituitary–adrenal (HPA) axis, the steroid cortisol is secreted in response to external and internal stressors in order to re-establish homeostasis[25]. Previous studies suggest that cortisol may serve as a potential short-term correlate of loneliness, predicting poor physical or mental health outcomes in the long-term[21,22].

According to the social buffering hypothesis[26], social relationships play a beneficial role in physical and mental health[26–29]. Among the most intense social relationships are romantic relationships, as they serve as the primary source of support, fulfilling needs such as intimacy, attachment, and emotional support[30]. Supportive and affectionate interactions with the partner reduce stress, pain, and psychological distress. They even influence the immune system, wound healing or mortality rates[31–35]. Being in a relationship has been found to be associated with lower loneliness levels, compared to never-married, divorced, and widowed individuals[36–38]. Especially in the middle and higher age, romantic relationships become important buffers for loneliness[39]. Additionally, romantic relationships directly affect physiological stress responses, such as cortisol secretion. Individuals who are in a close relationship, show lower aggregated cortisol levels than singles[40] and affectionate couple interaction can reduce cortisol levels[41,42]. On the other hand, the loss of a partner, for example due to breakup or death, is considered one of the most stressful life events in adulthood, being associated with reduced mental and physical health outcomes[43]. Divorced and widowed individuals show significantly higher loneliness scores than married individuals[44–46]. Moreover, partner loss is accompanied by altered HPA axis functioning, resulting in elevated cortisol levels and flattened diurnal cortisol slopes[47].

Although being in a relationship protects against feelings of loneliness, couples can also experience higher levels of loneliness. As one important factor, relationship quality has been shown to be negatively associated with loneliness[48–53]. In times of extreme social isolation, relationship quality might become an important moderator, especially if couples do not live together and thus are unable to see their partner and potentially have to rely on non-physical relationship qualities. Living alone has become increasingly prevalent, with one-person households accounting for more than 40% of all households in Scandinavian nations, more than 33% of all households in France, Germany, and England; and more than 25% of all households in the United States, Russia, Canada, Spain, and Japan[54]. In Germany, in the young adult age of 18 to 30 years, more than 30% live without a partner[55]. An important distinction in this context is between partnerships with and without a common household (the latter being called "living apart together"). In general, living alone has been seen as a risk factor for poor physical and mental health[54,56]. For instance, the living situation predicts mortality risk[57,58] and people who are living alone show higher loneliness levels[59]. Cross-sectional studies suggest that during the pandemic, being married served as a protective factor against loneliness[60], whereas being divorced or widowed increased the risk of loneliness[61]. Furthermore, living with others has been found to protect against loneliness[62], even when controlling for relationship status[63] and loneliness during lockdown predicted psychological distress[64]. However, it has not been investigated yet, whether relationship status and living situation during lockdown affected biological, specifically neuroendocrine, health parameters, such as cortisol levels. In previous studies, living alone had been positively correlated with cortisol levels[65]. Likewise, the buffering effect of living situation and relationship status with regard to psychobiological outcomes during stress-exposure (i.e. the world-wide considerable psychological stress through COVID-19) has not been examined yet. Previous research suggests that the separation from a partner is linked to elevated feelings of loneliness and cortisol levels in general[66–68]. In adolescents, significant correlations between self-reported loneliness and cortisol awakening responses during COVID-19 lockdown were found[69]. Nonetheless, moment-to-moment associations of loneliness and cortisol have not been investigated in adults yet. Furthermore, it is still elusive if relationship status and living situation moderate these associations. Lastly, the effect of psychological variables such as relationship satisfaction, on the association between living arrangements and loneliness during lockdown has not yet been addressed.

Study objectives. The purpose of this study was to investigate relationship status and living situation as potential moderators for trait and state loneliness as well as momentary cortisol levels during the COVID-19 pandemic and during lockdown. We aimed to replicate findings about the association between relationship status and trait loneliness, showing that being in a relationship is associated with lowest levels of loneliness, followed by singlehood and divorce/widowhood (Hypothesis 1). In order to explore state loneliness and cortisol in every-day life, we used an ecological momentary assessment (EMA) approach. Secondly, we expected that the current living situation and relationship status have an impact on momentary (state) loneliness (Hypothesis 2) and cortisol levels (Hypothesis 3). Based on previous studies[59–69], we assumed that being in a relationship and living with others are associated with lower loneliness and cortisol compared to being single and living alone. Additionally, we hypothesized a positive association between momentary (state) loneliness and momentary (state) cortisol levels (Hypothesis 4) and expected the relationship status and living situation to moderate this association (Hypothesis 5). Specifically, we hypothesized that being in a relationship and living with others buffers the effects of momentary loneliness on cortisol levels. Lastly, we hypothesized that relationship quality moderates the association between living situation and momentary (state) loneliness levels in individuals being in a relationship (Hypothesis 6). More precisely, we expected that the negative effect of living apart together on loneliness is buffered through high relationship quality.

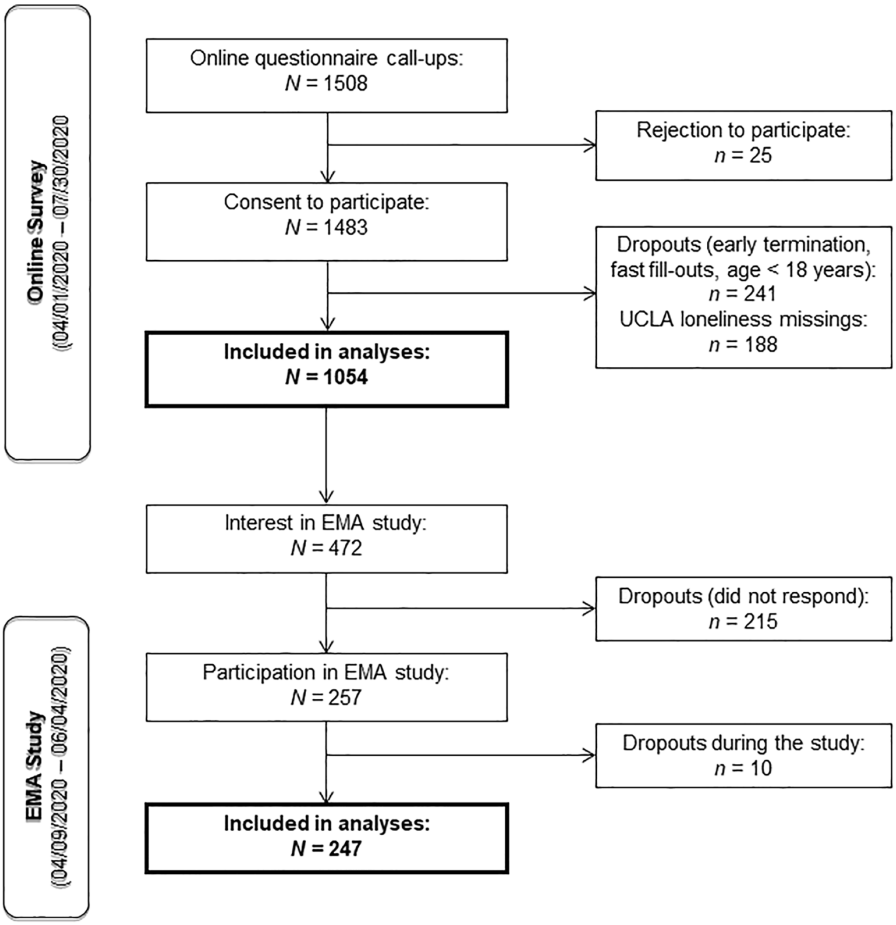

Figure 1. Flowchart of the recruitment process. *Note.* Participants were recruited between April 1st and July 30th 2020 via online media and local newspapers. Inclusion criteria were: Fluency in German, minimum age of 18 years and willingness to participate voluntarily. In total, 1483 individuals agreed to participate, from which 1054 participants filled out the questionnaires of interest.

Methods

Participants. This study was approved by the Heidelberg Medical Faculty's Ethics Committee (Heidelberg University, approval no. S-214/2020) and performed in accordance with the Declaration of Helsinki. All participants signed an informed consent and were recruited between April 1st and July 30th 2020 via online media and local newspapers. Inclusion criteria were: Fluency in German, minimum age of 18 years and willingness to participate voluntarily. In total, 1483 individuals agreed to participate, from which 1054 participants filled out the questionnaires of interest (see Fig. 1). The mean age of the participants was $M = 36.32$ years ($SD = 14.75$, $Range = 18; 81$), with 77.7% being female ($n = 819$). Demographic characteristics are displayed in Table 1.

Of the participants in the online survey, 472 showed interest in the EMA with the salivary sampling. Of those 472 participants, 54% ($n = 257$) took part in the EMA study. After excluding individuals who did not react to our messages and dropouts during data collection ($n = 10$), the remaining 247 cases were included in the analyses. The participants' mean age was $M = 32.6$ years ($SD = 13.12$, $Range = 18; 78$), with 70% being female ($n = 173$). Demographic characteristics of the EMA study sample are displayed in Table 2.

Measures. *Loneliness.* To measure trait loneliness in the online survey, we employed the German version of the revised 20-item University of California at Los Angeles (UCLA) loneliness scale[70,71]. Within our study, the scale displayed high internal consistency (Cronbach's $\alpha = .91$). Participants are asked to answer, how often they felt a certain way during the past two weeks, on a 4-point Likert scale with higher scores indicating more loneliness. Exemplary items are 'I feel isolated from others.' or 'I do not feel alone.' (negatively scored item). In order to assess momentary levels of loneliness in the EMA study, we used a single item measure ("Do you feel lonely at the moment?") with a visual analogue scale (VAS; 0—not at all, to 100—very lonely).

	Categories	*n* (%)
Gender	Female	819 (77.7)
	Male	227 (21.5)
	Diverse	4 (.4)
	Non-responders	4 (.4)
Occupation	At school/training/college/university	368 (34.9)
	Employed/civil servant	502 (47.6)
	Self-employed	100 (9.5)
	Unemployed	40 (3.8)
	Pensioner/housewife/househusband	98 (9.3)
Relationship status	In a relationship	655 (77.7)
	Single	329 (31.2)
	Divorced/widowed	70 (6.6)

Table 1. Demographic characteristics of study 1 (online survey). This table depicts total and relative sample sizes split in different groups (gender, occupation and relationship status) of the Online-Study. Total $N = 1054$. Participants in the singles group are those who were never-married.

	Categories	*n* (%)
Sex	Female	173 (70)
	Male	74 (30)
Relationship status	In a relationship	171 (69.2)
	Single	71 (28.7)
	Missing	5 (2)
Living situation	Living alone	52 (21.5)
	Living with others	194 (78.5)
Relationship status × living situation	Single—living alone	26 (10.5)
	Single—living with others	45 (18.2)
	In a relationship—living alone	26 (10.5)
	In a relationship—living with others	70 (28.3)
	In a relationship—living with partner	75 (30.4)
	Missing	5 (2)

Table 2. Demographic characteristics of the EMA study. This table depicts total and relative sample sizes split in different groups (gender, relationship status, living situation and relationship status depending on living situation) of the EMA study. Total $N = 247$. Participants in the singles group are those who were never-married.

Salivary cortisol. Saliva samples for determination of cortisol concentrations were collected at the same times as EMA. Sampling times were adapted to the individual wake-up time. Samples were taken at six time-points on two consecutive days: directly after awakening, 30 min, 45 min, 2½ h and 8 h after awakening and immediately before going to sleep. Participants stored the samples in their freezer until collected on dry ice and stored at − 80 °C until analysis. Analyses were conducted in the biochemical laboratory at Heidelberg University Hospital's Institute of Medical Psychology using commercial enzyme-linked immunosorbent assay (ELISA, Demeditec Diagnostics, Germany) procedures with reported detection limit of .019 ng/mL. Intra- and interassay variability for cortisol were 2.95% and 7.51% respectively. Log-transformed (ln) momentary as well as mean cortisol levels were used as outcome measures.

Relationship quality. Relationship quality was assessed via the short version of the *Partnerschaftsfragebogen* (PFB)[72]. It consists of 9 items that can be answered on a 4-point Likert scale. In our sample, the internal consistency of the PFB was very good (Cronbach's $\alpha = .85$). We used the global PFB score by adding up all items. The total score ranges between 0 and 36.

Control variables. For both trait and state loneliness as outcome, we included age and sex as control variables (CVs), as they have been previously shown to influence loneliness during the lockdown[73]. For momentary cortisol as outcome, CVs were assessed on both the momentary level and the trait level, based on expert consensus guidelines[74,75]. The following CVs were assessed on a momentary level: sleep duration, sleep quality, sleeping problems, sleep medication, forced awakening, brushing teeth, eating behaviour, drinking behaviour, medication, alcohol consumption, nicotine consumption, caffeine consumption, and physical activity (with respect to the last sample), assessment time-point (1 variable for the rise from time-point 1 to 2, and 1 variable for the fall

from time-point 2 to 6), and day (1 vs. 2). Trait level control variables were age, sex, and body mass index (BMI). As the momentary level CVs were of a high number and we wanted to reach a somewhat parsimonious model, we first determined, which of the theoretically included CVs had an impact on cortisol at all. We thus run an initial hierarchical linear regression with momentary cortisol levels as outcome and all CVs as predictors. The variables that had no significant association with cortisol levels ($p > .05$) were excluded from our final analyses. Significant CVs for cortisol as outcome were: eating, drinking, alcohol consumption, caffeine and physical activity (yes/no). As the results of the more parsimonious model and the full model were identical, we decided to report on the parsimonious model for easier interpretation. However, both models are included in Appendix B.

Procedure. The study was part of a large-scale longitudinal study that aims to investigate long-term consequences of COVID-19 lockdown on psychobiological health. Results within this paper entail data from time-point 1 (first lockdown in Germany). The online survey as well as the EMA were both conducted with the platform *soscisurvey.de* and participation was completely anonymous. After completing the online survey, participants were asked whether they wanted to take part in the EMA. Those who were interested, were contacted via email. The responders received Salicap® tubes for saliva collection with additional informational documents via mail and specific instructions via phone. The assessment of the saliva samples took place between April 9th and June 3rd 2020. On two consecutive days, the participants received the respective link via SMS to a short online survey including instructions for saliva sampling six times per day. Participants were asked to refrain from food or caffeine before they provided three saliva samples which were stored in the freezer. Then, they were asked to answer further questions about their sleeping behaviour, consumption behaviour, and physical activity. Commitment was constantly monitored online: if the participants have not yet accessed the link 5 min after it was sent, they were reminded by phone to do so. After completion of the two sampling days, data were stored on an institute-internal data server and saliva samples remained in the participants' home freezer until collection.

Data processing and statistical analyses. Hypotheses 1–3 focused on between-person effects and only included level 2 predictors (relationship status and living situation). Thus, these hypotheses were tested with analyses of covariance (ANCOVA). For hypothesis 1, family status (married/in a romantic relationship vs. single vs. divorced/widowed) served as independent variable (IV) and UCLA loneliness scores as dependent variable (DV). Post-hoc contrasts coding was conducted in order to analyse the linear trend of the means. For hypotheses 2 and 3, relationship status (single vs. in a relationship) and living situation (alone vs. with others) served as IVs. In this step we were interested in overall loneliness and cortisol in every-day life, thus the aggregated momentary loneliness and cortisol levels were used as DVs. As the distribution of the cortisol data was positively skewed, we natural-log-transformed the data in order to normalize their distribution. In case the assumptions of conducting an ANCOVA were violated, we used bootstrapping estimates ($n = 1000$) in order to achieve more robust results[76]. To test pairwise differences in momentary loneliness scores between the living situation and relationship status groups (in case the main effects were significant), we calculated Tukey Honestly Significant Differences (HSD) with Bonferroni-corrected p values adjusted for multiple comparisons. We further calculated partial η^2 in order to receive the effect sizes, with $\eta^2 \geq .01$ indicating a small, $\eta^2 \geq .06$ a medium, and $\eta^2 \geq .14$ a large effect.

As hypotheses 4 and 5 included a cross-level interaction, we conducted multilevel modelling (MLM) regression analyses, which enabled us to assess the within- and between-person effects of momentary loneliness on momentary cortisol levels. By using MLM we were able to represent the hierarchical structure of the data, which was necessary in order to depict the multilevel-predictors. The individual levels of loneliness were centred on the person's mean in order to test the within-person effect on cortisol levels. In order to assess the between-person effects, we centred the individuals' mean loneliness levels on the grand mean. For hypothesis 5, relationship status (single vs. in a relationship) and living situation (living alone vs. living with others) were included as dichotomous moderators in order to assess their interaction with level 1 loneliness scores (the exact formulas for hypotheses 4 and 5 are displayed in Appendix A in the supplement). For hypothesis 6, we conducted an ANCOVA with the sub-dataset of participants in a relationship, using living situation (alone vs. not alone), grand-mean-centred relationship quality (PFB) and their interaction as predictors, as well as age and sex as covariates. ANCOVA analyses were conducted with SPSS Statistics Version 27 ©, whereas MLM analysis were conducted via R Version 4.0.3.

Results

In the following, we will report results from all hypotheses separately. Descriptive statistics of the outcomes of interest are shown in Tables 3 and 4, respectively.

Trait loneliness depending on family status (Hypothesis 1). On average, participants had a loneliness score of $M = 38.95$ ($SD = 10.89$; $Range = 20–77$). There was a significant effect of family status on trait loneliness after controlling for sex and age ($F(1, 1035) = 26.67$, $p < .001$, $\eta^2 = .049$). Sex was significantly related to self-reported loneliness, with women showing higher loneliness scores than men ($F(1, 1035) = 6.39$, $p = .012$, $\eta^2 = .006$). The subsequently planned contrasts revealed a significant linear trend ($F(2, 1035) = 26.67$, $p < .001$, $\eta^2 = .049$), indicating that married people/people in a relationship displayed the lowest loneliness scores, followed by singles and divorced/widowed individuals.

Association of relationship status and living situation with loneliness in every-day life (Hypothesis 2). Participants in the EMA study reported an overall loneliness of $M = 27.36$ with highly varying scores ($SD = 20.94$).

Results indicate significant associations of both living situation ($F(1, 234) = 12.93$, $p < .001$, partial $\eta^2 = .05$) and relationship status ($F(1, 234) = 8.57$, $p = .004$, $\eta^2 = .04$) with mean loneliness levels. People living alone reported

Groups	Trait loneliness (UCLA loneliness scale)	
	M	*SD*
Family status		
Married/in a relationship	37.2	9.75
Single	41.09	11.91
Divorced/widowed	45.42	12.03
Sex		
Male	37.18	10.15
Female	39.33	10.95

Table 3. Means and standard deviations of the UCLA loneliness scale (online survey). This table depicts means (*M*) and standard deviations (*SD*) of trait loneliness, measured by the UCLA loneliness scale, in the different subgroups of the online-study.

Groups	State loneliness (VAS)	
	M	*SD*
Living situation		
Living alone	37.55	23.44
Living with others	24.63	19.42
Relationship status × living situation		
Single—living alone	39.29	25.6
Single—living with others	32.32	23.28
In a relationship—living alone	35.74	21.35
In a relationship—living with others	23.09	18.99
In a relationship—living with partner	21.42	15.99

Table 4. Means and standard deviations of momentary loneliness levels (EMA study). This table depicts means (*M*) and standard deviations (*SD*) of momentary (state) loneliness, measured by a single-item measure with a VAS scale (0–100), in the different subgroups of the EMA study.

significantly higher loneliness than people living with others. Also, individuals who were in a relationship reported significantly lower loneliness levels than singles. A third ANCOVA yielded a significant interaction between living situation and relationship status on mean loneliness ($F(1, 233) = 7.27$, $p < .001$; $\eta^2 = .11$). Post-hoc Tukey's HSD test indicated significant differences for the following pairwise comparisons (see Fig. 2): in a relationship living alone versus in a relationship living with partner ($p = .016$), single living with others versus in a relationship living with partner ($p = .028$), single living alone versus in a relationship living with partner ($p = .001$), in a relationship living alone versus in a relationship living with others ($p = .056$), and single living alone versus in a relationship living with others ($p = .005$).

Association of relationship status and living situation with cortisol in every-day life (Hypothesis 3). Descriptive statistics of the variables of interest are displayed in Table 5. Mean cortisol levels in the entire EMA-sample were $M = 8.6$ ng/mL ($SD = 2.22$). Results show a significant effect of relationship status on mean cortisol levels ($F(1, 219) = 4.58$, $p = .034$, partial $\eta^2 = .02$), with singles having significantly higher mean cortisol levels than individuals with a partner. Living situation did not have a significant effect on mean cortisol levels ($F(1, 219) = .04$, $p = .840$). Furthermore, BMI had a significant effect on cortisol, with higher BMI levels predicting higher cortisol levels ($F(1, 219) = 15.16$, $p < .001$).

Association of momentary loneliness, relationship status, and living situation with cortisol levels (Hypotheses 4 and 5). The Intraclass Correlation Coefficient (*ICC*) within the empty MLM was .007, indicating that .7% of the variance in cortisol levels was accounted by between-person differences and 99.3% by within-person differences. As 22 cases had missing values on level 2 variables, a total of 225 cases and 1722 data points were included in the analyses. The random intercept and slopes model (with level 1-loneliness set as random predictor) showed a better fit to the data compared to the random intercepts-only model, ($\chi^2(2) = 7.52$, $p = .020$), therefore we report results from this model. There was a non-significant within-person effect of self-reported loneliness on cortisol levels ($b = .002$, $t(1487) = 1.34$, $p = .179$). Importantly, we observed a significant interaction between relationship status and momentary loneliness levels ($b = -.004$, $t(1487) = -2.88$,

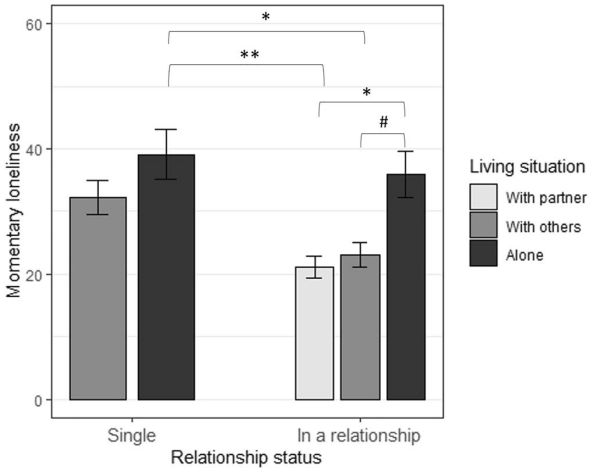

Figure 2. State loneliness levels (visual analogue scale) as a function of relationship status and living situation in the EMA study. *Notes.* Results of the Tukey's HSD test assessing differences in mean loneliness levels of the EMA sample as a function of relationship status and living situation. ** represents $p < .001$, * represents $p < .05$, and # represents $p < .1$. Error bars depict confidence intervals based on the *t*-distribution.

Groups	Cortisol (ng/mL)	
	M	*SD*
Relationship status		
In a relationship	8.44	6.13
Single	8.98	6.31
Living situation		
Living alone	8.64	2.31
Living with others	8.61	2.19

Table 5. Means and standard deviations of salivary cortisol levels (EMA study). This table depicts means (*M*) and standard deviations (*SD*) of momentary cortisol levels, measured by a single-item measure with a VAS scale (0–100), in the different subgroups of the EMA study.

$p = .004$). Therefore, the association between a person's momentary loneliness levels and momentary cortisol levels was smaller for participants who were in a relationship than for those who were single. Pseudo R^2 for this interaction was .1315, showing that the amount of unexplained variance in cortisol levels was reduced by 13.15%. The interaction between living situation and momentary loneliness levels was not significant ($b = .002$, $t(1487) = .96$, $p = .361$). Results of the reduced model (with significant CVs only) and the full model (with all CVs) are shown in supplementary Tables 1–4 in Appendix B in the supplements.

Relationship satisfaction as moderator of the associations between living arrangements and loneliness (Hypothesis 6). In the subsample of participants who were in a relationship, participants displayed self-reported mean relationship quality of $M = 20.22$ ($SD = 4.87$; *Range* = 6–27). ANCOVA revealed a significant association between relationship quality and self-reported mean state loneliness levels ($F(1, 149) = 5.02$, $p = .03$, $\eta^2 = .03$)). Furthermore, participants who were living alone, showed significantly higher state loneliness levels compared to participants who were living with others ($F(1, 149) = 9.77$, $p = .002$, $\eta^2 = .06$). However, the interaction between relationship quality and living situation was not significant ($F(1, 149) = 1.97$, $p = .16$, $\eta^2 = .01$), indicating that relationship quality did not moderate the association between living situation and loneliness.

Discussion

This study examined the (separate and joint) associations between structural (relationship status and living situation), psychological factors (relationship quality) and loneliness and cortisol during COVID-19 lockdown.

All in all, our results provide further evidence for the belongingness-hypothesis, showing that romantic relationships, as a source for meaningful interactions and intimacy, as well as living with others protect against loneliness and neuroendocrine stress-responses, in this case diurnal cortisol levels[36–38,54,59]. Moreover, divorced/widowed participants showed the highest trait loneliness, followed by singles (never-married). Thus, the loss of previously experienced positive relationship aspects such as romantic support, solace, and physical proximity,

may be associated with feelings of loneliness. Furthermore, individuals who were in a relationship and living alone ("living apart together"), were lonelier than those who were living with their partner, but did not differ in their momentary loneliness levels compared to singles living alone. Being in a relationship and living with others was associated with similar levels of loneliness compared to being single and living with others. This indicates that, during extreme physical isolation and contact restrictions, having a partner per se does not protect against loneliness, but rather living with others becomes an increasingly important buffer for loneliness. As during hard lockdown, intimacy and physical closeness are lacking in couples who are living apart, these important stress-buffering factors in the romantic relationship are suddenly missing, which is experienced as aversive[68]. Contrary to this finding, Greenfield and Russel found higher loneliness levels in couples who were living apart but with others[59]. One explanation for these conflicting findings could be that during lockdown, there were no alternatives for direct social interactions outside the apartment and thus the co-habitants became an especially important substitute for any direct contact with the romantic partner. We further found that higher relationship quality predicted lower momentary loneliness levels, which is in line with cognitive approaches to loneliness assuming that quality rather than quantity of social relationships buffers short-term psychological burden. However, relationship quality did not moderate the association between living situation and loneliness. Thus, the protective effect of living together during the COVID-19 lockdown was evident irrespectively of the relationship quality. In the online survey, female participants reported significantly higher trait loneliness levels than male participants. This adds to numerous studies revealing female gender as a risk factor for loneliness[77,78]. Interestingly, however, recent neuroimaging studies indicate that loneliness-associated neural effects may be more pronounced in high lonely men than women[79,80].

Although the results support our hypotheses about the importance of structural and psychological factors for self-reported loneliness, there are many other potential psychological mediators explaining these associations. It is important to keep in mind that romantic relationships buffer against negative mental and physical health consequences only under certain circumstances, for instance if marital functioning is perceived as positive[33]. Moreover, social dimensions such as perceived social proximity, knowing that there is someone you can count on, as well as actually perceived support, may be important underlying mechanisms influencing psychobiological health[29].

On a neuroendocrine level, being in a relationship buffered momentary cortisol levels and their association with loneliness. This is also in line with theoretical and empirical literature indicating that having a romantic partner serves as a biological *zeitgeber*. It has been suggested that social interactions on a regular and high frequent basis help regulating optimal physiological stimulation levels by modulating arousal to be medium high and attenuating maladaptive stress[81]. These results show us that romantic relationships have a direct impact on neuroendocrine stress responses, which in a long-term may have a positive effect on health-related outcomes[21,22]. Contrary to our hypothesis, living arrangements by themselves neither affected cortisol levels nor moderated the association between momentary loneliness and cortisol levels. One reason why these associations were only found with relationship status, could be, that there may be operators that are unique in relationships. For instance, feelings of connectedness[82], intimacy[41] or affective touch[83] are specific driving factors in romantic relationships. As they are not characteristic for other relationships such as co-habitants, they only come into use when romantic relationships are investigated.

This study adds to previous research on social buffering[17,26,27,29] in the context of enduring stress and extreme physical isolation. As lockdown-related long-term psychological health problems are increasingly revealed, it is important to study structural and psychological factors that might influence those consequences. Likewise, short-term neuroendocrine responses during lockdown could help unravel the neurobiological mechanisms underlying detrimental effects of loneliness and social isolation for mental health. Using a psychobiological EMA design, we were able to assess not only trait loneliness levels, but also moment-to-moment variations in loneliness and salivary cortisol in a naturalistic setting. The every-day life assessments took place in the individuals' personal environments, which yielded highly ecologically valid data. Moreover, as the participants' current loneliness levels were directly assessed, reporting errors due to retrospective assessment could be reduced. In order to represent the hierarchical structure of the data, MLM was used, enhancing statistical power of the analyses. Moreover, due to the close supervision of the participants, we were able to keep their commitment high and thus collect high-quality data. Another strength of this study is the wide range of the participants' age, making the sample more representative for every age group. The collection of saliva samples in the participants' every-day life enabled us to integrate psychobiological measures and provide a multi-level view on stress experiences during COVID-19.

This study has several limitations that need to be addressed. First of all, sample sizes differed between relationship subgroups due to recruitment of a convenience sample, reducing statistical power of the analysis and potentially biasing the results. As widowers/widows and divorced individuals are on average older and less technically involved than singles, they are more difficult to recruit for an online survey. To address this problem, we analyzed the data using bootstrapping and non-parametric test. Both analyses revealed comparable results. Noteworthy, sensitivity analyses show that only medium but not small effect sizes could have been reliably detected within our sample. Thus, the results should be interpreted with caution. Another limitation is the cross-sectional design of the study, which makes it impossible to draw causal conclusions on long-term (mental) health outcomes. Furthermore, there is no baseline assessment of the variables of interest before lockdown, therefore we were not able to control for the participants' pre-lockdown levels of loneliness and cortisol. Thus, our results can only be seen as a "snapshot" of the current situation. In addition, the data collection during this specific phase of lockdown in which the majority of participants worked from home hampers generalization of our data to other situations.

There are several aspects that could be addressed in future research. Although we found main effects of relationship status, living situation, and relationship quality, they only explained a small amount of variance in the outcomes. This indicates that there are additional predictor and moderator variables influencing the outcomes. For example, previous research has shown that level of education of the own partner has an influence on mental and physical health[84]. Additionally, the stress-buffering effects of close relationships is not restricted to romantic

relationships. For example, having meaningful relationships with close friends or relatives[38] could be one protective factor. In addition, longitudinal assessments with repeated within-person measurements of loneliness and cortisol over a longer period of time could be implemented, in order to probe long-term psychological and physiological consequences of COVID-19 and strict lockdowns.

All in all, our study reveals further evidence for romantic relationships as a protective factor against trait and state loneliness, both on a structural level (alone vs. in a relationship) and a psychological level (relationship quality), as well as momentary cortisol levels during the ongoing stress of the pandemic and social isolation. Additionally, living with others during lockdown protects against loneliness in every-day life. The fact that individuals who were living apart from their partner displayed similar levels of loneliness compared to singles, implicates that especially in times of social isolation, the lack of direct physical contact to the partner makes a difference when it comes to psychological burden. This joint role of partnership and living situation should be taken into account when analysing structural factors for negative mental health outcomes, but also identifying resources for resilience. Moreover, it is especially important to consider not only relationship status, but also relationship quality as an important psychological aspect of romantic relationships and a buffering factor for loneliness in couples, potentially counter-balancing the negative effects of living alone. This is in line with previous epidemiological research suggesting that rather than being married, it is the satisfaction with the relationship (e.g., the amount of support or criticism from a partner), which influences health-related outcomes[85]. In the context of clinical interventions, the results implicate that especially singles and divorced individuals, women, couples with low relationship quality as well as alone living residents (whether single or in a relationship) should be offered psychosocial support in order to prevent them from long-term negative health consequences. More importantly, on the one hand, individuals who are living apart from their partner, could profit from interventions to enhance their perceived relationship quality, on the other hand, alone living single individuals should be offered help in re-establishing meaningful social bonds with their close friends in order to counter-regulate their feelings of loneliness. Finally, public health campaigns should address and sensitize the society towards loneliness and mental health symptoms in those different groups to empower individuals to actively approach social offers and use them as resource.

Data availability

The datasets generated during and/or analysed during the current study are openly available online (https://doi.org/10.11588/data/SYVQMM).

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3.3. Publication 3: Lonely in the Dark: Trauma Memory and Sex-Specific Dysregulation of Amygdala Reactivity to Fear Signals

RESEARCH ARTICLE

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Lonely in the Dark: Trauma Memory and Sex-Specific Dysregulation of Amygdala Reactivity to Fear Signals

Mitjan Morr, Jeanine Noell, Daphne Sassin, Jule Daniels, Alexandra Philipsen, Benjamin Becker, Birgit Stoffel-Wagner, René Hurlemann, and Dirk Scheele**

Loneliness exacerbates psychological distress and increases the risk of psychopathology after trauma exposure. However, it is still unclear whether a lack of social connectedness affects trauma-related intrusions and the neural processing of fear signals. Moreover, it is uncertain, whether loneliness plays a different role in women and men. A prestratification strategy is used and $n = 47$ ($n = 20$ women) healthy lonely individuals and $n = 35$ controls ($n = 18$ women) are recruited. Participants are exposed to an experimental trauma and evoked intrusive thoughts in daily life are monitored for three consecutive days. Functional magnetic resonance imaging is used to assess neural habituation to fearful faces and fear learning (conditioning and extinction) prior to trauma exposure. The results reveal a significant interaction between loneliness and sex such that loneliness is associated with more intrusions in men, but not in women. A similar pattern emerges at the neural level, with both reduced amygdala habituation to repeated fearful faces and amygdala hyperreactivity during the conditioning of fear signals in lonely men. The findings indicate that loneliness may confer vulnerability to intrusive memories after trauma exposure in healthy men and that this phenotype relates to altered limbic processing of fear signals.

1. Introduction

Loneliness, defined as the discrepancy between desired and actual social connectedness,[1] is a growing problem in modern societies.[2] Loneliness can be considered as the social equivalent to hunger or pain to meet social needs and has been associated with increased mortality, resembling risk factors like obesity or smoking.[3,4] Furthermore, loneliness is closely linked with various psychiatric disorders such as substance abuse, depression, and anxiety disorders.[5,6] Importantly, loneliness also constitutes a risk factor for developing post-traumatic stress disorder (PTSD) following a traumatic experience.[7,8] In fact, loneliness predicts future PTSD and is predicted by past PTSD symptoms, indicating a bidirectional relationship between PTSD and social connectedness.[9,10]

PTSD is a debilitating and frequently chronic condition characterized by intrusive thoughts about the traumatic experience as a key symptom.[11–13] Intrusions are defined as involuntarily spontaneous memories of the distressing incident, mainly experienced as visual forms of mental imagery.[14–16] The lifetime prevalence of PTSD varies substantially between sexes, with women being twice as likely to develop PTSD than men.[17] Current neurocircuit models of PTSD highlight dysfunction of the amygdala–hippocampus complex as a core mechanism underlying the persistence of intrusive memories. Modern trauma-focused

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psychotherapies for treating intrusions and other PTSD symptoms often include an exposure-based intervention to reduce fear responses.[18] Mechanistically, this decrease in fear responses can be achieved by both fear extinction and fear habituation. The former is characterized by a progressive decrement of a conditioned fear response (CR) when a conditioned stimulus (CS) is repeatedly presented in the absence of an aversive unconditioned stimulus (UCS) with which it has previously been paired, while the latter is based on repeated exposure to the (imagined) UCS. In fact, both fear extinction and habituation recruit overlapping forebrain structures including the amygdala.[19]

The experimental trauma paradigm is a widely used and reliable method to evoke intrusions by showing traumatizing film footage in a controlled laboratory setting.[14,20,21] On a neural level, increased reactivity in the amygdala, hippocampus, insula, and anterior cingulate cortex during trauma exposure predicts increased intrusive thoughts.[22,23] Interestingly, neural processing during fear extinction has also been linked to intrusion frequency in an experimental trauma paradigm and reduced extinction capacity predicts PTSD development.[24,25] Furthermore, women reported more intrusive symptoms following the trauma paradigm than men, and this sex difference was related to peritraumatic responding and slowed extinction learning in women.[26] Likewise, women showed a sustained amygdala response to negative evocative images relative to men.[27]

We previously found that strong trauma disclosure reduces intrusions and alters amygdala functional connectivity following trauma exposure only in individuals with heightened concentrations of the hypothalamic peptide oxytocin after intranasal administration.[28] Given a crucial role of oxytocin in safety learning and a reduced oxytocin reactivity to positive social interactions in people experiencing loneliness,[29,30] this raises the intriguing possibility that loneliness influences intrusions after trauma exposure by modulating self-disclosure and amygdala-related fear processing. Furthermore, a recent large-scale study indicated a higher prevalence of loneliness in men than in women,[31] and a growing number of studies reported sex-specific effects of loneliness. For instance, loneliness was associated with more pronounced within-network coupling of the default network in men than in women, and brain volume effects in the limbic system were linked to the frequency and intensity of social contact in a sex-dependent manner.[32–34] Surprisingly, however, the impact of loneliness on fear conditioning/extinction and fear habituation as well as the possible moderation by sex remain unclear. Therefore, this study aimed to examine loneliness-associated neurobiological risk factors for intrusive thoughts in an experimental prospective study design.

To this end, we recruited a prestratified sample of 82 healthy volunteers assigned to either a high-lonely and low-lonely group to test how loneliness interacts with sex to influence the neural processing of fear signals and the formation of intrusive thoughts. During functional magnetic resonance imaging (fMRI), subjects completed an emotional face-matching task to assess neural responses to fearful faces and the habituation of these responses. In addition, we used a classical Pavlovian fear conditioning and extinction paradigm with two social and nonsocial stimuli one of each paired (CS+) and one without (CS−) an electric shock. To explore hormonal group differences, blood samples were taken before the fMRI session. Subsequently, we probed psychological (dissociative symptoms, state anxiety, positive and negative affect), physiological (electrodermal activity, pupil sizes), and hormonal (oxytocin) stress responses during an experimental trauma paradigm. The trauma paradigm consisted of a 24-min-long aversive video to mimic trauma exposure. Furthermore, evoked intrusions and communication behavior were monitored via online diaries during three consecutive days after trauma exposure. The total number of intrusions, trauma disclosure (i.e., desire to talk and talk duration), intrusion stress ratings and the level of amygdala reactivity in neural fear processing served as primary study outcomes. We hypothesized that lonely individuals would exhibit more pronounced responses to the experimental trauma film and experience more intrusions. Furthermore, we expected to observe loneliness-dependent hyperreactivity to fearful faces and fear-conditioned stimuli in the amygdala, as well as changes in functional connectivity in a network responsible for fear processing.[35–37] Given previous findings about sex differences in the effects of loneliness and the formation of intrusive memories, we explored sex as a moderator variable.

2. Results

2.1. Subclinical Psychiatric Symptoms, Loneliness, and Sex Differences

Psychiatric symptoms were measured via questionnaires during a screening interview. In addition, blood samples were taken before fMRI scanning. High-lonely subjects reported more depressive symptoms, alexithymia, childhood maltreatment, social interaction anxiety, and subjective stress compared to low-lonely participants (all ps < 0.02; shown in Table S7, Supporting Information). Furthermore, high-lonely participants had smaller and less diverse social networks and received less social support (all ps < 0.03). In addition, across groups, women reported having more social support than men ($F_{(1,78)} = 5.12$, $p = 0.03$, $\eta_p{}^2 = 0.06$). There were no significant interactions between sex and loneliness in psychiatric symptoms and social network quality (all ps > 0.05). Besides the expected sex differences, we found a significant sex*loneliness interaction in estradiol levels ($F_{(1,65)} = 7.60$, $p = 0.01$, $\eta_p{}^2 = 0.11$), showing that high-lonely women exhibited higher estradiol levels than low-lonely women at the fMRI session ($t_{(16.55)} = 2.62$, $p_{cor} = 0.04$, $d = 0.87$; shown in Table S1, Supporting Information). For a detailed list of differences in psychiatric symptoms between groups see **Table 1**.

2.2. Psychological and Physiological Reaction to the Trauma Video

An experimental trauma paradigm was conducted after the fMRI. Dissociative symptoms, positive and negative affect, state anxiety, and saliva oxytocin were measured before and after trauma exposure via questionnaires and saliva samples. Physiological stress markers (pupil size and electrodermal activity) were measured during trauma exposure. After trauma exposure, subjects showed dissociative symptoms (mean ± SD = 1.24 ± 1.18, one-sample t-test against zero: $t_{(77)} = 9.36$, $p < 0.01$, $d = 1.06$) and reported high arousal (76.87 ± 23.53) induced by and low valence (9.35 ±

Table 1. Baseline differences between the high-lonely and low-lonely groups (Notes: Values are the mean and SD in brackets).

	Women			Men		
	High-lonely (n = 20)	Low-lonely (n = 18)	t	High-lonely (n = 27)	Low-lonely (n = 17)	t
Loneliness[a)]	54.60 (5.62)	23.56 (1.20)	24.09**	55.19 (3.53)	24.06 (1.03)	43.00**
Depressive symptoms[b)]	4.25(3.51)	2.11(3.64)	1.84	3.85 (3.91)	1.53 (2.15)	2.54*
Social anxiety[c)]	22.20 (17.20)	13.39 (9.85)	1.96	22.52 (18.99)	11.82 (15.40)	1.95
Childhood maltreatment[d)]	35.00 (9.43)	32.11 (15.32)	0.71	38.44 (10.06)	29.47 (5.30)	3.86**
Alexithymia[e)]	41.15 (9.53)	32.39 (6.46)	3.29**	46.22 (10.43)	34.29 (6.54)	4.21**
Social support[f)]	60.40 (9.50)	68.11 (3.10)	3.43**	52.11 (12.88)	65.59 (12.88)	3.38*
Perceived stress[g)]	13.25 (7.09)	8.78(5.11)	2.21*	12.96 (6.48)	7.35 (4.64)	3.1**
Trait anxiety[h)]	36.95 (7.71)	27.67 (5.13)	4.31**	40.15 (9.82)	26.35 (4.76)	6.23**
Social network[i)]						
Numbers	18.35 (9.18)	21.22 (7.58)	1.05	14.04 (5.40)	19.35 (7.31)	2.77*
Roles	5.30(1.56)	5.78(1.44)	0.98	4.56 (1.05)	5.65 (1.62)	2.72*
Networks	1.80(1.40)	2.22(1.06)	1.04	1.33 (1.00)	2.06 (1.20)	2.17*

[a)] Participants were prestratified and assigned to the high- or low-lonely group using the UCLA Loneliness Scale (UCLA-L). High-lonely participants had a score equal or above 50, while low-lonely participants had a score equal or below 25; [b)] Depressive symptoms were measured with the Beck Depression Inventory, Version II (BDI); [c)] Social anxiety was assessed with the Liebowitz Social Anxiety Scale (LSAS); [d)] Childhood traumata were measured using the Childhood Trauma Questionnaire (CTQ); [e)] Alexithymic symptoms were assessed by the Toronto Alexithymia Scale (TAS); [f)] Social Support was measured with the Social Support Questionnaire ((Fragebogen zur sozialen Unterstützung); F-SozU); [g)] Perceived stress was quantified by the Perceived Stress Scale (PSS-10); [h)] Trait anxiety was assessed by the State Trait Anxiety Inventory (STAI); [i)] Social network was characterized using the Social Network Index assessing the number of diverse social roles, networks, and the total number of people to whom the participants talk to regularly. Group differences were calculated by two-sample t-tests. **, $p < 0.01$; *, $p < 0.05$.

16.16) of the trauma film. Neither dissociative symptoms nor valence and arousal were affected by loneliness or sex (all ps > 0.05). Subjects showed a decrease in positive affect (main effect of time: $F_{(1,72)} = 67.88$, $p < 0.01$, $\eta_p^2 = 0.49$; shown in **Figure1**A) and an increase in negative affect (main effect of time: $F_{(1,72)} = 139.58$, $p < 0.01$, $\eta_p^2 = 0.66$; shown in Figure 1B) independent of sex and loneliness following the trauma video. In addition, state anxiety increased significantly (main effect of time: $F_{(1,72)} = 154.91$, $p < 0.01$, $\eta_p^2 = 0.68$; shown in Figure 1C) and we observed an interaction between loneliness and time ($F_{(1,72)} = 4.44$, $p = 0.04$, $\eta_p^2 = 0.06$), such that lonely individuals displayed higher baseline state anxiety ratings ($t_{(76)} = 4.42$, $p_{cor} < 0.01$, $d = 1.02$) than low-lonely individuals, but state anxiety significantly increased in both groups (high-lonely: $t_{(41)} = 8.98$, $p < 0.01$, $d = 1.39$; low-lonely: $t_{(33)} = 7.99$, $p < 0.01$, $d = 1.37$).

Physiologically, there was an increase in the skin conductance level (main effect of time: $F_{(1,61)} = 13.57$, $p < 0.01$, $\eta_p^2 = 0.18$; shown in Figure 1D) and pupil size ($F_{(1,65)} = 133.96$, $p < 0.01$, $\eta_p^2 = 0.67$; shown in Figure 1E) compared to baseline. Furthermore, salivary oxytocin levels significantly increased after trauma exposure ($F_{(2130)} = 3.39$, $p = 0.04$, $\eta_p^2 = 0.05$; post hoc t-test: $t_{(72)} = 4.05$, $p_{cor} < 0.01$, $d = 0.47$; shown in Figure 1F). Thus, the trauma video elicited a psychological and physiological stress response regardless of sex and loneliness.

2.3. Intrusive Thoughts

The primary study outcomes, intrusive thoughts, trauma disclosure (desire to talk, talk duration), and intrusion stress ratings were measured via online questionnaires on three consecutive days after trauma exposure. Across loneliness groups, women experienced more intrusions than men (main effect of sex: $F_{(1,77)} = 8.53$, $p = 0.01$, $\eta_p^2 = 0.10$). However, our results revealed a significant interaction between loneliness and sex ($F_{(1,77)} = 5.57$, $p = 0.02$, $\eta_p^2 = 0.07$), such that loneliness was associated with more intrusive memories in men but fewer intrusions in women (shown in **Figure 2**A). Post hoc t-tests further revealed that low-lonely women exhibited significantly more intrusions than low-lonely men ($t_{(33)} = 3.97$, $p_{cor} < 0.01$, $d = 1.39$), while there was no significant sex difference in high-lonely individuals ($t_{(44)} = 0.39$, $p = 0.70$, $d = 0.12$). Furthermore, analysis of the desire to talk about the trauma movie yielded a pattern consistent with intrusion effects ($F_{(1,65)} = 5.62$, $p = 0.02$, $\eta_p^2 = 0.08$; shown in Figure 2B). High-lonely woman showed a decreased desire, whereas high-lonely men exhibited an increased desire in contrast to low-lonely individuals. Again, post hoc t-tests revealed that low-lonely women showed an increased desire to talk in contrast to low-lonely men ($t_{(32)} = 2.66$, $p_{cor} = 0.046$, $d = 0.91$). In addition, high-lonely subjects talked less about the movie (main effect of loneliness: $F_{(1,49)} = 9.85$, $p < 0.01$, $\eta_p^2 = 0.17$; shown in Figure 2C), indicating that the sex-specific association of loneliness with the desire to talk about the traumatic experience did not lead to a similar pattern in actual trauma disclosure. Neither sex nor loneliness significantly affected intrusion stress ratings (all ps > 0.05).

2.4. Emotional Face-Matching: fMRI Effects

fMRI scanning was conducted before trauma exposure and consisted of an emotional face-matching task and a fear conditioning and extinction paradigm. In the emotional face-matching task, participants had to match two simultaneously presented pictures at the bottom with a target picture presented at the top of the

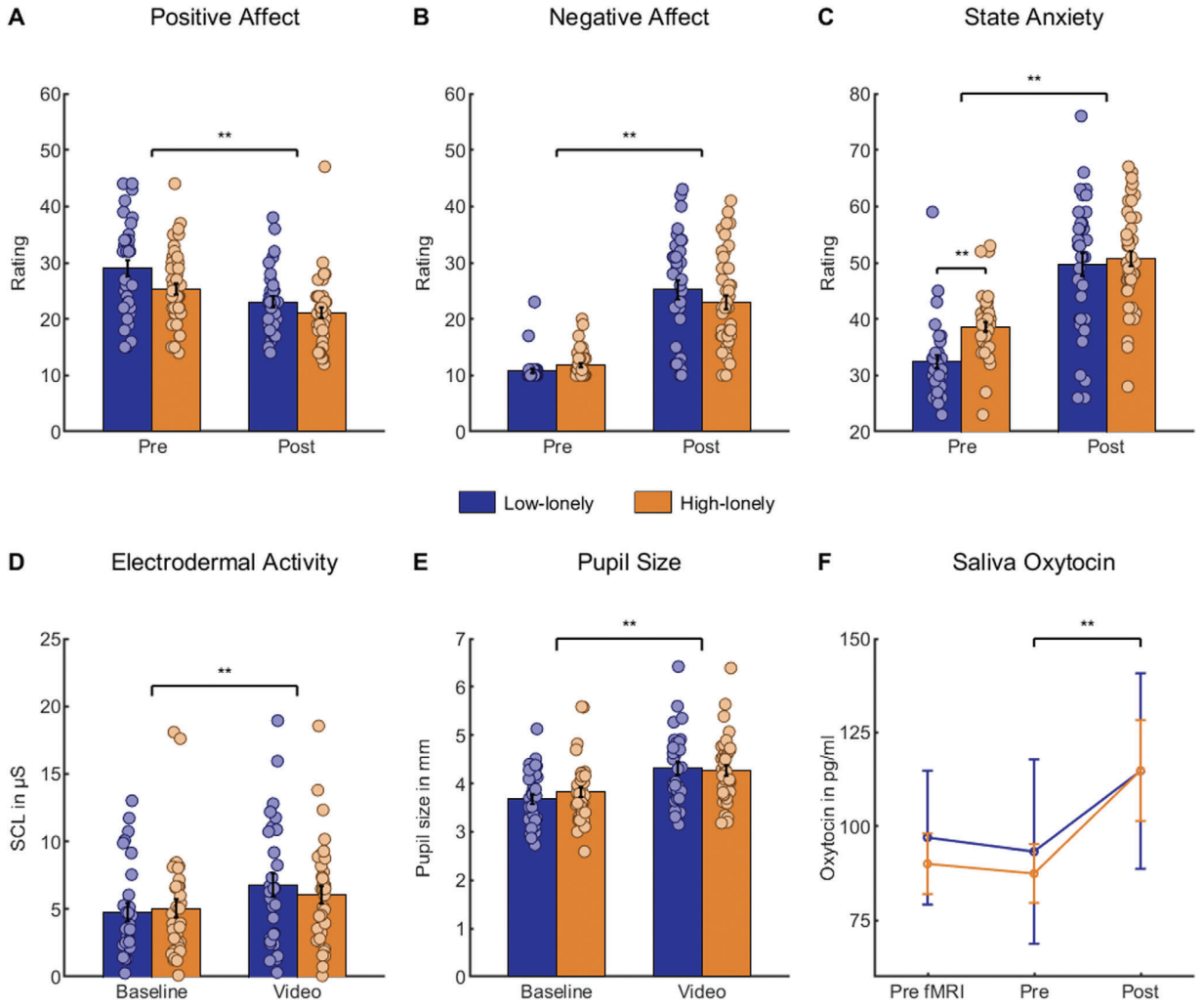

Figure 1. Acute psychosocial and physiological responses to the trauma paradigm were comparable across groups. Affect measured by the Positive and Negative Affect Schedule (PANAS) changed significantly, such that positive affect decreased ($t_{(75)} = 8.13$, $p < 0.01$, $d = 0.74$, $n = 76$; A), while negative affect increased ($t_{(75)} = 11.48$, $p < 0.01$, $d = 1.89$, $n = 76$; B). Anxiety before the video measured by the State Trait Anxiety Inventory (STAI) was increased in high-lonely subjects ($t_{(76)} = 4.42$, $p < 0.01$, $d = 1.02$, $n = 78$; C) and increased across groups ($t_{(75)} = 11.49$, $p < 0.01$, $d = 1.65$, $n = 76$; C). Physiological arousal was evident in increased skin conductance levels ($t_{(64)} = 3.67$, $p < 0.01$, $d = 0.36$, $n = 65$; D) and pupil sizes ($t_{(68)} = 11.28$, $p < 0.01$, $d = 1.36$, $n = 69$; E) during the video. Furthermore, saliva oxytocin levels increased significantly after trauma exposure ($t_{(72)} = 4.05$, $p_{cor} < 0.01$, $d = 0.24$, $n = 73$; F). Error bars show the standard error of the mean (SEM). Abbreviations: Pre, directly before the trauma paradigm; Post, directly after the trauma paradigm; Pre fMRI, directly before the functional magnetic resonance imaging; SCL, skin conductance level. *P*-values for time effects were calculated by paired sample *t*-tests. Loneliness effect in state anxiety was calculated by a two-sample *t*-test; ** $p < 0.01$.

screen. In the fear conditioning and extinction paradigm, participants had to press a button before the UCS to indicate if they believed that they would receive an electric impulse. Responses were acquired with an fMRI compatible response grip system to measure reaction times and contingency ratings. Amygdala reactivity in both paradigms served as primary study outcome. There was no significant interaction effect of sex and loneliness on the neural response to fearful faces per se, but amygdala habituation was characterized by sex*loneliness interactions. Habituation to fearful faces in the right amygdala was reduced in high-lonely men compared to high-lonely women, while this pattern was reversed in low-lonely individuals (interaction sex*loneliness: Montreal Neurological Institute $(MNI)_{xyz}$: 34, 2, −22, $F_{(1,75)} = 12.72$, $p_{FWE} = 0.04$; Fearful $_{Block\ 1}$ > Fearful $_{Block\ 3}$; shown in **Figure 3**A). Across groups, right amygdala habituation to fearful faces correlated negatively with the number of intrusions ($r_{(76)} = -0.22$ $p = 0.049$; Fearful $_{Block\ 1}$ > Fearful $_{Block\ 3}$). In addition, a significant sex*loneliness interaction was observed for the left amygdala habituation to all faces which was reduced in high-lonely women compared to high-lonely men and the opposite pattern was evident in low-lonely individuals (MNI_{xyz}: −30, −2, −22, $F_{(1,75)} = 17.53$, $p_{FWE} = 0.01$; Faces $_{Block\ 1}$ > Faces $_{Block\ 3}$).

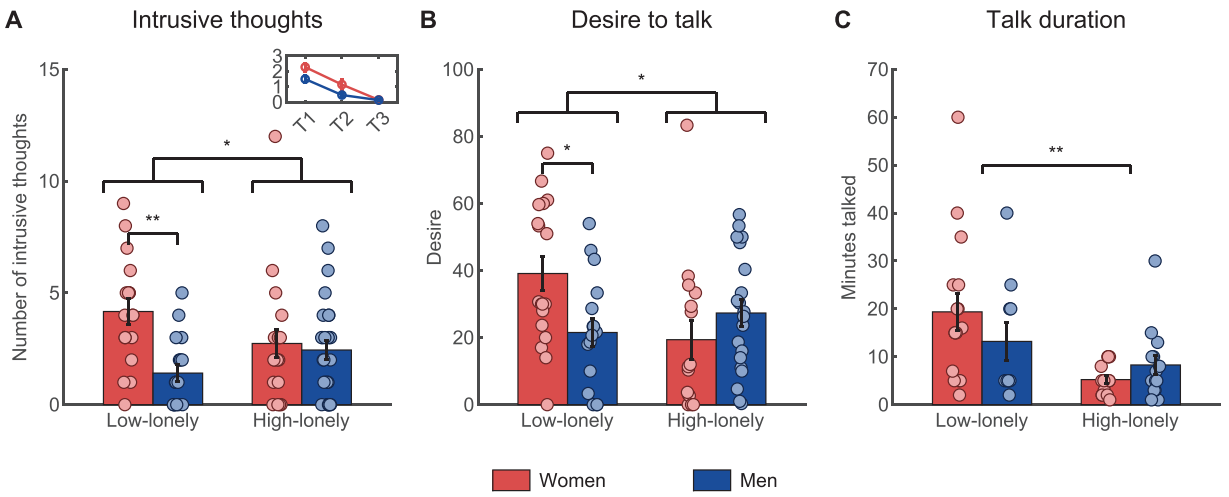

Figure 2. High-lonely men experienced more intrusions than low-lonely men in the three days following the trauma video, while this pattern was reversed in women (interaction effect: $F_{(1,77)} = 5.57$, $p = 0.02$, $\eta_p^2 = 0.07$, $n = 81$; A). The inlay shows the decrease in intrusions over the following three days. High-lonely men showed an increased desire to talk about the experience (from 0 = no desire to 100 = extreme desire) in contrast to low-lonely men. Women showed the reversed pattern (interaction effect: $F_{(1,65)} = 5.62$, $p = 0.02$, $\eta_p^2 = 0.08$, $n = 69$; B). Furthermore, high-lonely subjects talked less about their traumatic experience regardless of sex (main effect of loneliness: $F_{(1,49)} = 9.85$, $p < 0.01$, $\eta_p^2 = 0.17$, $n = 53$; C) Error bars show the standard error of the mean (SEM). Abbreviations: T1–T3, days after trauma exposure. *P*-values were calculated by mixed-design ANOVAs with fixed factors sex and loneliness and by two-sample *t*-tests. * $p < 0.05$; ** $p < 0.01$.

Further habituation analyses revealed a sex*loneliness interaction in functional connectivity. High-lonely men showed increased right amygdala coupling with the left superior parietal lobe in the habituation process to fearful faces (MNI_{xyz}: −34, −52, −58, $k = 108$, $p_{FWE} = 0.01$; Fearful $_{Block\ 1}$ > Fearful $_{Block\ 3}$; shown in Figure 3B) in contrast to high-lonely women, while this pattern was reversed in low-lonely individuals. Collectively, amygdala habituation and functional connectivity in high-lonely men seemed to be most pronounced in response to fearful stimuli, whereas amygdala habituation in high-lonely women seemed to be altered regardless of the emotional valence of the social stimuli. Further behavioral and neural results of the emotional face matching task are reported in in Tables S2 and S3 of the Supporting Information.

2.5. Fear Conditioning and Extinction: Contingency Ratings

Successful conditioning was evident in higher contingency ratings of the CS+ compared to the CS− in the second half of the COND (conditioning) task (interaction effect of time (first half, second half) and condition (CS+, CS-): $F_{(1,64)} = 54.79$, $p < 0.01$, $\eta_p^2 = 0.46$). Likewise, a significant time*condition interaction ($F_{(1,63)} = 49.23$, $p < 0.01$, $\eta_p^2 = 0.44$) for the contingency ratings showed reduced shock expectations in the course of the EXT (extinction) task (shown in Table S5, Supporting Information). In addition, a time*condition interaction with sex and loneliness was evident such that high-lonely men showed higher contingency ratings (i.e., expected more electric shocks) to the CS+ in the second half of the COND phase than high-lonely women (time*condition*sex*loneliness; $F_{(1,64)} = 5.41$, $p = 0.02$, $\eta_p^2 =$ 0.08). There were no significant interactions with the factor sociality or sex * loneliness interactions in the EXT phase.

2.6. Fear Conditioning and Extinction: fMRI Effects

In the COND phase, the CS+ elicited activations in a fear conditioning network[35] including the amygdala (COND $_{CS+\,>\,CS-}$ MNI coordinates and statistics are listed in Table S5, Supporting Information). Importantly, amygdala reactivity to fear signals in the early phase of COND compared to that in EXT was associated with loneliness in a sex-specific manner (sex*loneliness interactions: MNI_{xyz}: 30, 0, −20, $F_{(1,72)} = 12.62$, $p_{FWE} = 0.046$; COND $_{CS+\,>\,CS-}$ > EXT $_{CS+\,>\,CS-}$; shown in **Figure 4**A). This effect was driven by a sex*loneliness interaction in the COND phase (MNI_{xyz}: 30, 4, −20, $F_{(1,72)} = 14.37$, $p_{FWE} = 0.02$; COND $_{CS+\,>\,CS-}$). High-lonely men exhibited higher amygdala activation than high-lonely women, while this effect was reversed in low-lonely individuals.

We also observed a loneliness*sex interaction in the functional connectivity of the amygdala during fear conditioning/extinction. High-lonely men exhibited a stronger coupling between the left amygdala and orbitofrontal cortex (MNI_{xyz}: −44, 28, −16, $k = 98$, $p_{FWE} = 0.02$; COND $_{CS+\,>\,CS-}$ > EXT $_{CS+\,>\,CS-}$; shown in Figure 4B) compared to high-lonely women during the conditioning of fear signals and this pattern was reversed for low-lonely individuals.

Importantly, including psychiatric symptoms that differed between groups (shown in Table 1; Table S7, Supporting Information), social support, hormonal contraception, and estradiol levels as covariates did not change the significant sex*loneliness interactions observed for intrusions and parameter estimates of

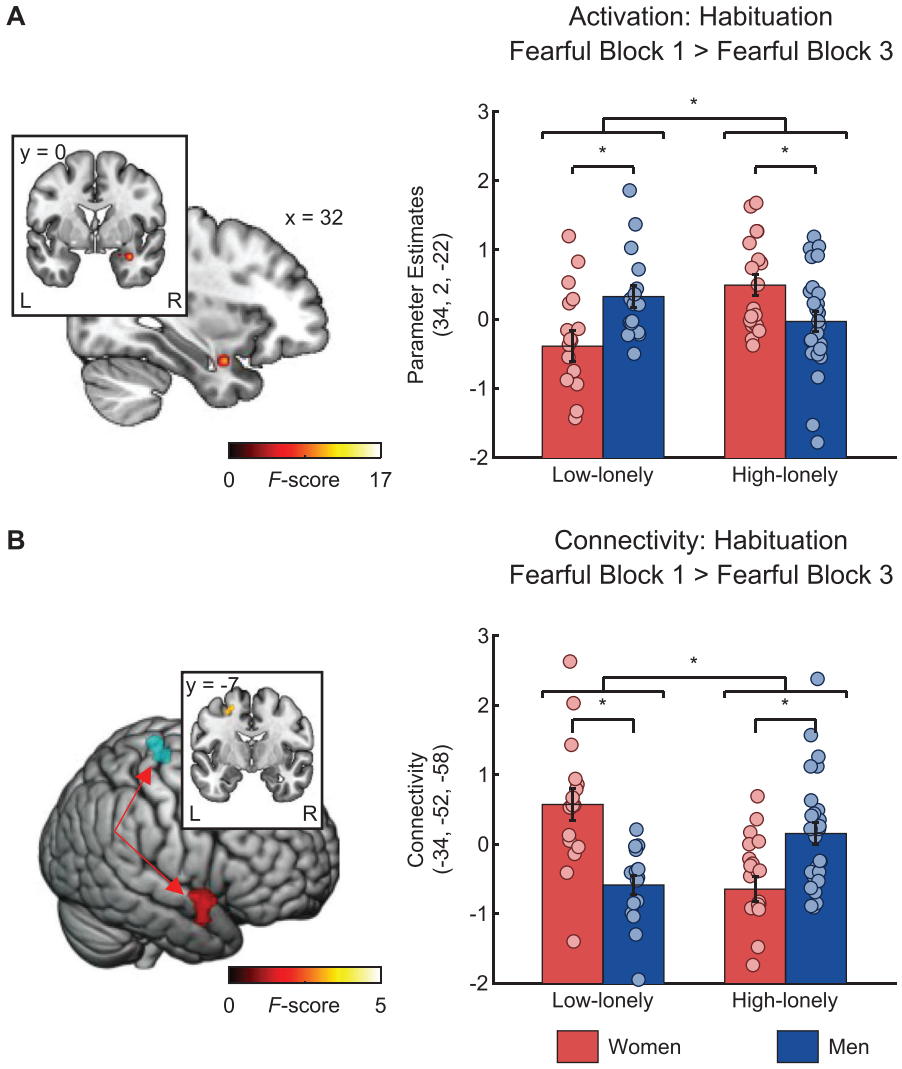

Figure 3. High-lonely men showed decreased right amygdala habituation (MNI_{xyz}: 34, 2, −22, $F_{(1,75)} = 12.72$, $p_{FWE} = 0.04$, $n = 79$; A) to fearful faces in contrast to high-lonely women and this pattern was reversed in low-lonely individuals. In addition, increased coupling between the right amygdala (red cluster) as the seed region and left superior parietal lobule (blue cluster; MNI_{xyz}: −34, −52, −58, $k_{(1,75)} = 108$, $p_{FWE} = 0.01$; $n = 79$; B) was observed during fear habituation in high-lonely men compared to high-lonely women, whereas this pattern was again reversed in low-lonely individuals. Coordinates are in MNI space. Error bars show the standard error of the mean (SEM). Abbreviations: L, left; R, right. *P*-values were calculated by mixed design ANOVAs with the fixed factors sex and loneliness and post hoc two-sample *t*-tests. * $p < 0.05$.

significant clusters (see the Supporting Information). Taken together, these findings indicate that fear habituation and conditioning mechanisms in an amygdala network vary as a function of loneliness and sex.

3. Discussion

The present study aimed to probe loneliness as a risk factor for increased physiological and psychological responses to an experimental trauma film. We further examined whether loneliness effects were moderated by sex and related to changes in the neural processing of fear signals. Our results revealed a significant interaction between sex and loneliness in intrusive thought formation such that loneliness was positively associated with more intrusions in men, but not women. A similar pattern emerged at the neural level, with both reduced amygdala habituation to repeated fearful faces and amygdala hyperreactivity during the conditioning of fear signals in high lonely men, but not in women. Our findings indicate that loneliness is indeed a risk factor for increased intrusions after trauma exposure in high-lonely men, and this relates to amygdala reactivity in a network responsible for fear conditioning and habituation in these vulnerable individuals.

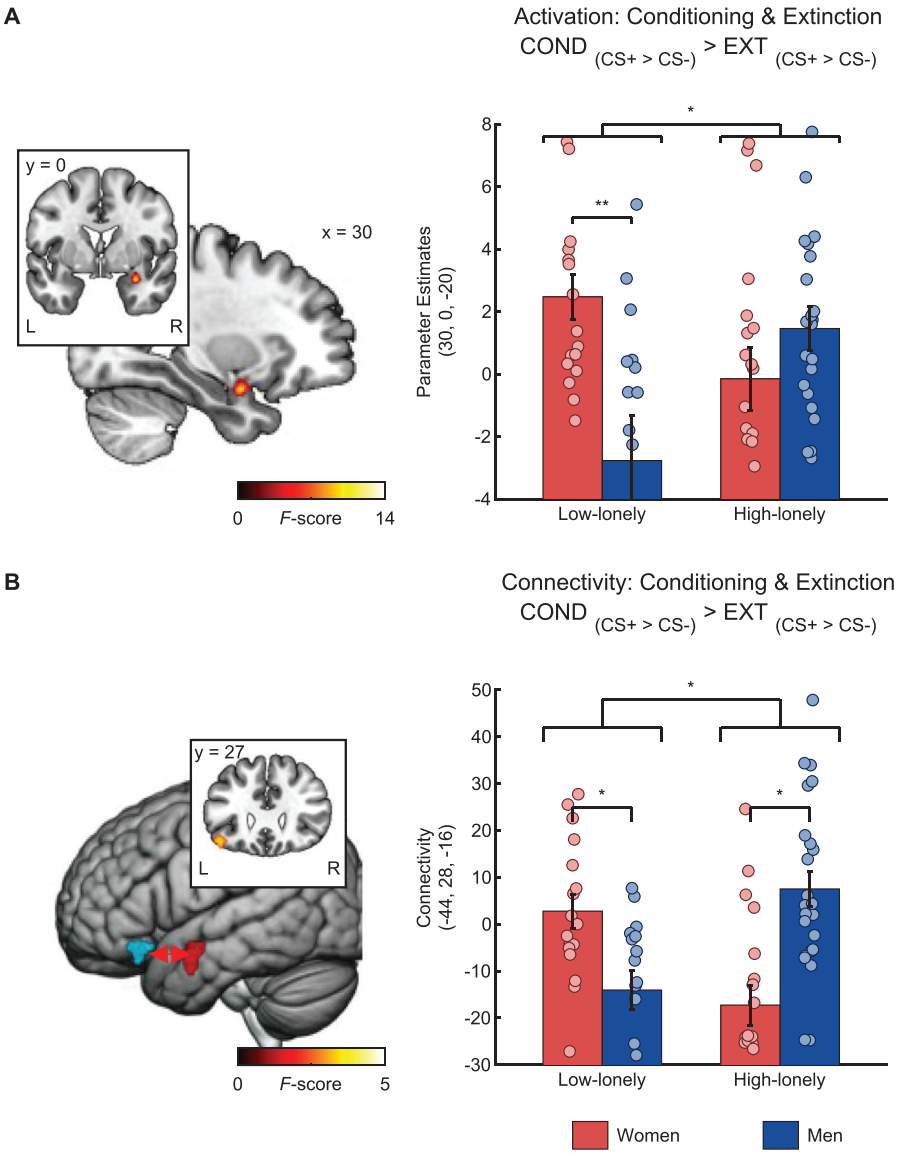

Figure 4. High-lonely men exhibited stronger right amygdala activity (MNI_{xyz}: 30, 0, −20, $F_{(1,72)} = 12.62$, $p_{FWE} = 0.046$, $n = 76$; A) during fear conditioning than high-lonely women and this pattern was reversed in low-lonely participants. Furthermore, connectivity between the left amygdala (red cluster) as the seed region and left orbitofrontal areas (blue cluster; MNI_{xyz}: −44, 28, −16, $k = 98$, $p_{FWE} = 0.02$, $n = 76$; B) was increased during fear conditioning in high-lonely men compared to high-lonely women, and this pattern was again reversed in low-lonely participants. Coordinates are in MNI space, and error bars show the standard error of the mean (SEM). Abbreviations: COND, conditioning; CS+, fear-associated conditioned stimulus; CS−, non-fear-associated conditioned stimulus; EXT, extinction; L, left; R, right. *P*-values were calculated by mixed design ANOVAs with the fixed factors sex and loneliness and post hoc two-sample *t*-tests. * $p < 0.05$.

The experimental trauma paradigm elicited marked stress responses evident in significant psychological and physiological changes across all subjects. We did not observe significant loneliness or sex effects on these acute responses after the trauma film, indicating that loneliness may be more important in long-term coping with the traumatic experience. As expected, high-lonely subjects talked less about their traumatic experience than low-lonely individuals. Disclosure of emotional and traumatic events is known to reduce distress and may promote extinction of fear-related memories.[38,39] Furthermore, discussing traumatic memories reduces PTSD symptoms, and delayed disclosure predicts PTSD development.[40–43] Interestingly, reduced trauma disclosure cannot completely explain the loneliness-associated increase in intrusive thoughts observed in men, because high-lonely women also reported less trauma disclosure and experienced fewer intrusions than low-lonely women. In addition,

low-lonely women showed more intrusions than low-lonely men reflecting previously observed sex differences in intrusive thought formation.[26,44] In the current sample, in contrast to men, high-lonely women may be less vulnerable to trauma-induced intrusions since they also indicated less desire to talk about the trauma film relative to low-lonely women. Thus, sex-specific vulnerability to psychopathology may also vary depending on psychological factors such as social connectedness. The observed pattern of results could be related to our prestratification strategy and the recruitment of healthy high-lonely individuals who may be more resilient than high-lonely individuals who developed a psychological disorder. Along these lines, the opposing loneliness-related associations in women and men may have contributed to the absence of significant sex differences in high-lonely individuals. Therefore, in the same way that loneliness results from a discrepancy between desired and actual social connectedness, a mismatch between the desired and achieved trauma disclosure may be particularly important for individuals to cope with intrusive thoughts.

The amygdala is a well-known processing hub of fear-related stimuli and amygdala hyperreactivity is a risk factor for as well as a consequence of trauma-related disorders.[45–49] Sex-differences in amygdala lateralization and habituation have been previously observed, with women exhibiting more activity in the left hemisphere related to the subsequent memory for emotionally arousing images and showing more persistent bilateral amygdala responses to negative stimuli than men.[27,50,51] Intriguingly, low-lonely women showed significantly less amygdala habituation and experienced significantly more intrusions than low-lonely men and increased amygdala habituation correlated with reduced intrusions across groups. Our findings are consistent with previous studies that showed that decreased amygdala habituation is associated with heightened anxiety levels and PTSD symptom severity.[52–57] Furthermore, increased functional connectivity between the amygdala and the superior parietal lobe in high-lonely men may constitute a prospective risk factor for heightened intrusive thoughts since the parietal lobe is part of a common network responsible for intrusive thought formation.[58] Moreover, PTSD patients exhibit increased parietal activations during script-driven trauma imagery leading to dissociative responses.[59]

Furthermore, high-lonely men exhibited heightened amygdala responses to the CS+ and functional connectivity with the orbitofrontal cortex during conditioning compared to low-lonely men. Both amygdala and orbitofrontal cortex activity have been frequently linked to CS+/CS− differentiation during fear learning.[60] Nevertheless, increased amygdala responses to the CS+ were not reflected in significantly altered electrodermal activity (cf. the Supporting Information), indicating that the loneliness-related amygdala changes may be related to salience rather than arousal effects. The loneliness-related amygdala activation changes during habituation and conditioning in men were evident across social and nonsocial stimuli, which is in line with previous studies suggesting that loneliness fosters hypervigilance for threat cues.[4,61,62] Interestingly, high-lonely women compared to high-lonely men showed decreased left amygdala habituation to all faces, but we found decreased right amygdala habituation in response to social threat cues in high-lonely men. Impaired right amygdala habituation has also been previously identified as a neural phenotype of patients with borderline personality disorder and trauma exposure.[56] The absence of amygdala hypervigilance in high-lonely women could be driven by hormonal factors with high-lonely women showing increased estradiol levels compared to low-lonely women in our sample. Estradiol administration improved extinction recall after fear extinction,[63,64] and low levels of estradiol in women were linked to increased fear network responses to trauma films.[65] However, the observed sex differences cannot be completely explained by hormonal factors either because women reported more intrusions across loneliness groups despite having higher estradiol levels than men. It is conceivable that the content of the trauma film was more distressing for women than men, but we did not detect significant sex differences in the acute stress responses, and a previous study found no evidence for an interaction between sex and intrusive memories induced by different trauma films.[66] The unwillingness of men to admit loneliness and higher stigmatization of men who express feelings of loneliness might have contributed to the observed sex differences.[67,68] Taken together, our data suggest that loneliness has a sex-specific impact on the way threat cues are processed during fear conditioning and fear habituation.

The present study had several limitations. First, our sample consisted of women with and without hormonal contraception. Although we did control for the use of hormonal contraception and measured hormonal blood levels to control for menstrual cycle-related hormone changes, future studies are warranted to further delineate the hormonal basis of sex differences in the effects of loneliness. Second, the experimental trauma paradigm is widely used and well established to explore the neurobiological mechanisms underlying acute and prolonged trauma responses, but further clinical studies in a real-life setting are required to gauge whether our findings can be extrapolated to patients with trauma exposure. Third, while we found sex-specific associations between loneliness and amygdala reactivity consistently in two separate fMRI tasks, the results should be interpreted cautiously. The results were based on region of interest (ROI) analyses with lenient small-volume corrections and the effects sizes were small. Replication studies are warranted to test the robustness of these effects. Fourth, we used a prestratification approach and we only included individuals without current psychological disorders. This way we were able to exclude possible confounding effects due to current psychotherapy or pharmacotherapy. Nevertheless, given that loneliness is closely linked to mental health, the absence of loneliness-related effects in women may also reflect increased resilience in the group of high-lonely women.

Collectively, our results provide evidence that loneliness may confer vulnerability to increased intrusive thoughts in men following an experimental trauma. In addition, high-lonely men were characterized by an increased desire to talk about the trauma film and reduced actual trauma disclosure. This phenotype relates to altered limbic processing driven by amygdala hyperreactivity during fear conditioning and habituation. Based on these findings, secondary prevention strategies should take sex differences in loneliness into account and focus on improving the social connectedness of high-lonely men to mitigate the sequelae of traumatic experiences.

4. Experimental Section

Participants: The present study used a quasi-experimental design with a sample of prestratified healthy volunteers scoring high or low on the revised UCLA Loneliness Scale (UCLA LS).[69] High scorers (high-lonely) were defined by a score above or equal to 50 (i.e., at least one standard deviation above the mean score of healthy young adults,[70] which is similar to previous categorizations),[71] while low scorers (low-lonely) were defined by a score of 25 or below (i.e., at least one standard deviation below the mean). In total, 4515 participants completed the UCLA LS online questionnaire and a clinical screening interview was conducted with 97 subjects fulfilling the above-mentioned loneliness criteria. The final sample consisted of 82 healthy subjects (mean age ± standard deviation (SD): 26.39 ± 5.83 years) assigned to either a high-loneliness (n = 47 (20 women)) and a low-loneliness control group (n = 35 (18 women)). In accordance with our preregistration, every subject included in the final sample was aged between 18 and 46 years and had no current physical or psychiatric disorder as assessed via self-disclosure and the Mini-International Neuropsychiatric Interview,[72] no current psychotherapy, no current psychotropic medication, no illicit drug use in the previous four weeks, and was eligible for magnetic resonance imaging scanning (no pregnancy, metallic implants, etc.). All participants gave written informed consent. The study was approved by the institutional review board of the medical faculty of the University of Bonn (number 248/16) and carried out in compliance with the latest revision of the Declaration of Helsinki.

Experimental Design: In screening sessions, medical history and psychiatric symptoms were assessed (see the Supporting Information for inclusion criteria and Figure S1, Supporting Information, for a design overview). The testing session consisted of an fMRI scan containing a high-resolution structural scan, a fear COND/EXT paradigm,[73] and a well-established emotional face-matching paradigm.[74] All magnetic resonance imaging (MRI) data were acquired using a 3T Siemens TRIO MRI system (Siemens AG, Erlangen, Germany) with a Siemens 32-channel head coil. Following fMRI acquisition, the participants completed an experimental trauma paradigm.[28] To measure trauma disclosure and intrusive thoughts, subjects completed online diaries during the following three days after trauma exposure. Saliva samples were collected before the fMRI scan as baseline measure, and before and after the experimental trauma paradigm to measure oxytocin levels. In addition, blood samples were taken before the fMRI scan to measure the levels of gonadal steroids including estradiol and testosterone, as control variables. For a detailed list of the questionnaires and neuroendocrine parameters see the Supporting Information.

Emotional Face Matching Task: The first fMRI paradigm consisted of an adapted version of a well-established emotional face-matching paradigm.[74,75] Subjects had to match two simultaneously presented pictures at the bottom with a target picture presented at the top of the screen. Stimuli consisted of pictures of faces (neutral, fearful, and happy) and houses as nonsocial control stimuli. Stimuli were presented in three blocks for every condition (happy, fearful, and neutral faces, as well as houses), with each block consisting of five trials. Participants had to match the face identity (i.e., the emotion was consistent across all faces of a trial).

Fear Conditioning and Extinction Tasks: The COND/EXT paradigm was an adapted version of a Pavlovian fear conditioning paradigm described by Eckstein et al.[73] In the COND phase, subjects were shown four different pictures (two neutral faces (social stimuli) and two houses (nonsocial stimuli)). One social and one nonsocial pictures were designated as fear-associated CS (CS+) and the other picture of each category as safety signal (CS−). The choice of the picture that served as CS+ was counterbalanced within each group (high-lonely, low-lonely). Each stimulus was presented 16 times during the COND and EXT experiments. The trials were interleaved with an interstimulus interval (ISI) that was jittered between 5 and 7 s (mean: 6 s). In 75% of CS+ trials, subjects received an electric impulse (the UCS) 4 s after stimulus onset. The electric impulses were delivered by a Biopac System (MP150, Biopac Systems Inc., Goleta USA). To identify a stimulation intensity that was uncomfortable, but not painful, participants rated different intensities beforehand in an adaptive process (see the Supporting Information) while lying in the MRI on a scale from 0 to 100 (0 = not uncomfortable; 100 = most uncomfortable feeling imaginable). The stimulation intensity was set to reflect a rating of 60. In addition, the Biopac system measured electrodermal activity (EDA) and respiration during the experiment. After the COND phase, participants were informed that there would be another round of the same experiment. No electrical impulses were administered in the EXT phase. In both phases, participants had to press a button before the UCS to indicate if they believed that they would receive an electric impulse (i.e., a contingency rating was coded by +1 for an expected shock and −1 for no shock). For a detailed description of the data acquisition, preprocessing, and analyses of both tasks (see the Supporting Information).

Experimental Trauma Paradigm: Participants were seated in front of a Tobii TX300 binocular eye-tracker (Tobii AB, Danderyd, Sweden) with a 23 in display to measure pupil sizes as the outcome indicating physical arousal during the movie alongside EDA. To evoke intrusive thoughts, participants were confronted with a 24-min-long movie clip derived from the movie "I spit on your grave" showing the multiple rape of a young woman by a group of men. EDA data were measured with a Biopac MP150 system. Positive and negative affect, dissociative symptoms (measured with the dissociative symptoms scale),[76] valence (0 = low valence, 100 = high valence), arousal (0 = low arousal, 100 = high arousal) as well as state anxiety were measured prior and after the experimental trauma paradigm. The participants completed online intrusion diaries at home in the evening during three consecutive days following trauma exposure. For details about data collection and preprocessing, see the Supporting Information.

Online Diaries: The participants completed online intrusion diaries at home in the evening for three consecutive days after trauma exposure. In the intrusion diary, the participants stated the number of intrusions (defined as involuntary recollections relating to film events that appear, apparently spontaneously, in consciousness) and rated the distress caused by each of these intrusions on a visual analogue scale ranging from 0 (no distress) to 100 (extreme distress). Furthermore, participants were asked to state the time spent on talking about the trauma video (in minutes) and their desire (0 = no desire to 100 = strong desire) for trauma disclosure.

Statistical Analyses: The primary outcomes included the number of intrusions and blood oxygen level-dependent signal changes during fear learning and the processing of fearful faces. Fear habituation was assessed in an exploratory analysis. Other outcomes recorded were the psychological and physiological stress markers after trauma exposure and skin conductance response during fear conditioning. Mixed-design analyses of variance (ANOVAs) and Bonferroni-corrected (p_{cor}) post hoc t-tests were calculated using SPSS 25 (IBM Corp., Armonk, NY, USA) to examine changes in intrusive thoughts (sum of the three consecutive days following the trauma exposure), trauma disclosure (i.e., how long participants talked to other people and whether and how long they discussed the trauma movie with other people), group differences in psychiatric symptoms and psychological as well as physiological and hormonal responses to the trauma exposure with the between-subject factors of sex (women, men) and loneliness (high, low). Mixed-design ANOVAs for contingency ratings included the additional within-subject factors task (COND, EXT) and condition (CS+, CS−). Additional mixed-design ANOVAs for the COND/EXT paradigms included the between-subject factors of sociality (social, nonsocial) and time (first half, second half). Partial eta-squared and Cohen's d were calculated as measures of effect size.

To analyze the fMRI data, a two-stage approach was used as implemented in the MATLAB toolbox (The MathWorks Inc., Natick, MA) SPM12 (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). On the first level, data were modeled using a fixed-effects model. On the second level, the main contrasts of interest were compared between groups using a full factorial model with the two factors of loneliness and sex. Analyses were conducted using anatomically defined regions of interest (ROIs), including the amygdala, derived from the WFU PickAtlas (for further ROI results, see the Supporting Information). P values smaller than 0.05 after familywise error correction for multiple testing (p_{FWE}) based on the size of the ROI (i.e., small volume correction for separate ROIs) were considered significant. Whole-brain analyses were calculated across groups for task-validation (cluster defining threshold $p < 0.001$; significance threshold $p_{FWE} < 0.05$ corrected at

peak level). In addition, generalized psychophysiological interaction analysis was conducted to assess functional connectivity by using the CONN toolbox 18.a (www.nitrc.org/projects/conn, RRID: SCR_009550) with the same preprocessed data, ROIs, regressors, and contrasts that were used in the SPM analyses.[77] Parameter estimates of significant contrasts were extracted using MarsBar (https://www.nitrc.org/projects/marsbar, RRID: SCR_009605) and further analyzed in SPSS 25). Pearson correlations between parameter estimates of significant ROI clusters and intrusive thoughts were calculated.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

M.M. and D.S. designed the experiment. M.M., J.N., D.S., and J.D. conducted the experiments. M.M., B.S.-W., and D.S. analyzed the data. M.M. and D.S. wrote the manuscript. All authors read and approved the manuscript in its current version.

Data Availability Statement

The data that support the findings of this study are openly available in Open science framework at https://osf.io/np9wr/, reference number np9wr and Second level fMRI data are available at NeuroVault (https://neurovault.org/collections/HOUZNUPY/).

Keywords

amygdala, fear conditioning, fear habituation, loneliness, trauma memory

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3.4. Publication 4: Chronic loneliness: neurocognitive mechanisms and interventions

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Chronic Loneliness: Neurocognitive Mechanisms and Interventions

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Loneliness has been associated with detrimental effects on mental and physical health and is increasingly recognized as a critical public health issue which may be further exacerbated by societal challenges such as increasing urbanization, an aging society as well as the COVID-19 pandemic. A recent clinical study published in *Psychotherapy and Psychosomatics* has demonstrated that an internet-based cognitive behavioral therapy (ICBT) can significantly reduce loneliness, and such a preventive intervention may be co-opted to target suicidality in the elderly [1, 2]. As such, it is now an opportune time to review current conceptualization of chronic loneliness, its detrimental consequences and potential neurocognitive mechanisms as well as initial treatment strategies.

Loneliness is not a clinical diagnosis, but a psychological state with detrimental effects on physiological and mental health if it is experienced chronically. Prevalence estimates vary depending on the assessment criteria, but representative samples surveyed before the onset of the COVID-19 pandemic showed that 22% of inhabitants in the United States and 23% in Britain always or often feel lonely [3]. Loneliness can occur at any life stage, but elevated levels have been observed during late adolescence and in elderly people [4]. Various lines of research also indicate that the extended lockdowns and necessary social isolation during the COVID-19 pandemic have increased not only feelings of loneliness but also depression and suicidal ideation [5–7]. However, of note, loneliness is a subjective feeling which is distinct from objective social isolation [8, 9]. It is possible to have a large and diverse social network and feel lonely, and vice versa, to live a life with only a few meaningful social connections and experience no loneliness at all. Therefore, loneliness can be best described as a discrepancy between desired and actual social connectedness [10]. This conceptualization is in line with earlier epidemiological studies differentiating between "availability" and "adequacy" of social support. Increased mortality and risk of cardiovascular diseases have been linked to less perceived adequacy of social support [11–14]. In humans as a social species, loneliness may have evolved as an adaptive function and evolutionary coping strategy to promote behavioral changes, which increase the chance of survival [15]. Loneliness can be seen as a social equivalent to hunger, such that the feeling

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of loneliness triggers the need to form new social relationships, in the same way as hunger triggers the need to eat [16–18]. If loneliness is an evolutionary signal to form social bonds, the question of why some people stay lonely over extended periods of time arises. Current models of loneliness postulate that lonely individuals exhibit negative social biases which paradoxically lead to even more withdrawal from social connections [19]. Clearly, the effects of acute loneliness are distinct from the impact of chronic loneliness [20, 21]. For instance, a recent study found that chronic loneliness was associated with a greater preferred interpersonal distance, whereas acute loneliness was related to smaller preferred distances [22], possibly reflecting the evolutionary desire to form social bonds. Although previous studies found that acute social exclusion elicits activations in neural pathways overlapping with those mediating physical pain such as the dorsal anterior cingulate cortex (ACC) and may lead to severe distress [23, 24], a recent meta-analysis did not detect reliable activation in the dorsal ACC in acute social exclusion but rather found robust engagement of the ventral ACC, posterior insula, posterior cingulate cortex, and lateral prefrontal regions with further co-activation analyses demonstrating a functional co-variance with large-scale networks that resembled the default mode network (DMN) topography [25]. Nevertheless, acute social isolation should not be confused with chronic loneliness, which exerts more harmful effects such as strongly increased mortality in comparison to acute social isolation [26]. Chronic loneliness may function as a continuous psychological stressor which increases the allostatic load, characterized as the wear and tear resulting from chronic overreactivity of stress systems [27, 28]. Several studies linked satisfactory social relationships to reduced allostatic load [29–31]. Allostatic overload is associated with poor health and should be assessed with an integrated approach including not only clinimetric criteria but also biomarkers [32]. Several large-scale studies showed that common genetic variants contribute to loneliness in a range from 4 to 27% [33–35]. Therefore, loneliness seems to interact with a complex system consisting of individual biology, as well as psychosocial status and may lead to a form of biosocial pathogenesis [36, 37]. Given that the COVID-19 pandemic and the necessary measures of social distancing may facilitate the transition from acute to chronic loneliness [38], interventions in vulnerable populations [39] may help to reduce the allostatic load and therefore prevent the detrimental health consequences of loneliness.

Detrimental Health Consequences of Loneliness

Accumulating evidence from different lines of research convergently indicates the detrimental impact of chronic loneliness and perceived social isolation on both, somatic and mental health. A number of studies have established associations between chronic loneliness and increased morbidity and mortality mirroring the negative impact of well-established risk factors such as obesity or smoking. Thus, loneliness and social disconnection are increasingly recognized as major public health concerns [40–43]. Increasing evidence suggests associations between chronic loneliness and an impaired integrity of the immune system, including reduced numbers of natural killer cells [44, 45] and diminished immune responses to acute stressors [46] in lonely individuals. Chronic loneliness has also been linked to heightened blood pressure [47, 48] and an increased risk for coronary heart diseases and stroke [49, 50]. In addition, feelings of social isolation are a risk factor for obesity [51–53] and impaired sleep quality [54, 55]. Sleep deprivation in turn can trigger feelings of loneliness, starting a self-reinforcing cycle of social withdrawal [56]. Importantly, the detrimental effects of loneliness are not restricted to somatic disorders but extend to mental health. Perceived social isolation has been identified as a significant predictor for cognitive decline in dementia and Alzheimer disease [57, 58] and is associated with higher levels of depressive symptoms [59, 60], anxiety [61, 62], and psychosocial stress [63]. Furthermore, patients with substance abuse [64–66], borderline personality disorder [67, 68], and schizoid personality disorder [69] report more loneliness and social disconnection than healthy controls. In addition, loneliness is a potential risk factor for post-traumatic stress disorder [70, 71] and enhances intrusive thoughts after trauma exposure [72, 73]. Overall, loneliness and social isolation are critical risk factors for several somatic and mental disorders and thus should be considered in therapeutic protocols. The development of neurobiologically informed interventions for loneliness critically requires a better understanding of the brain structural and functional neural changes related to chronic feeling of social isolation.

Brain Structural Adaptations Associated with Loneliness

Prolonged periods of social isolation have been linked to broad changes in brain morphology. For instance, participants of a 14-month long Antarctica expedition exhib-

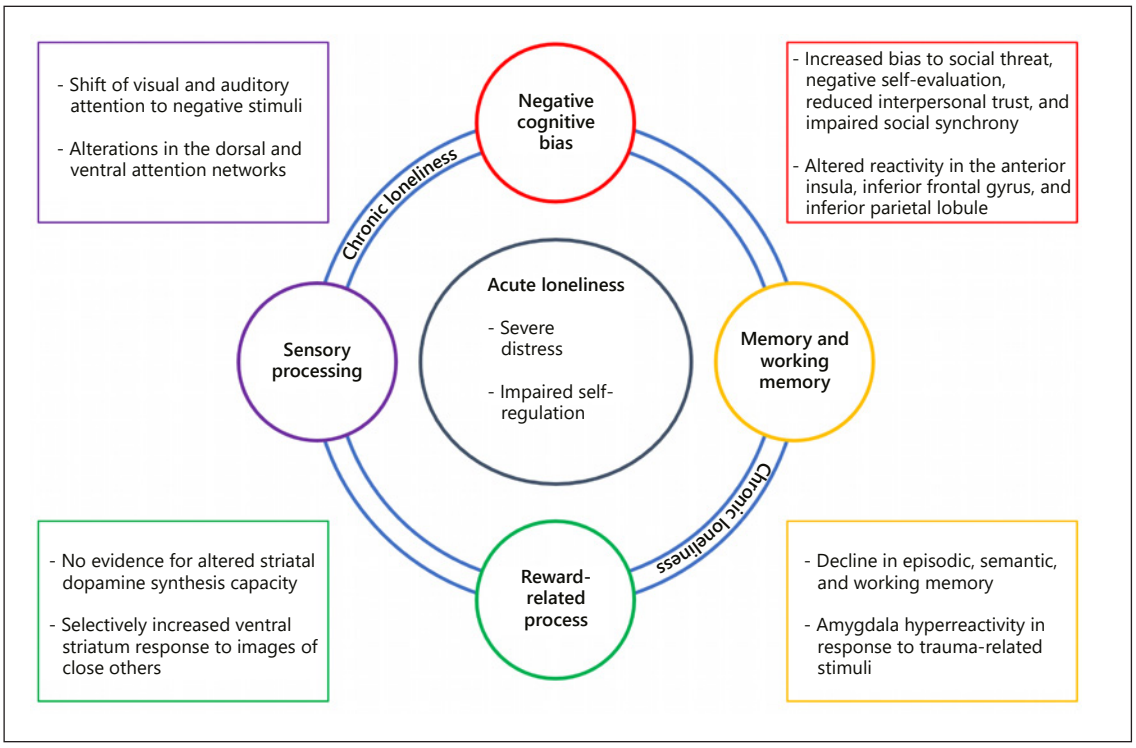

Fig. 1. Theoretical model illustrating the impact of acute and chronic loneliness. Acute effects of loneliness are shown in the inner circle. Chronic loneliness may affect functional domains which are illustrated in the outer circles. Exemplary findings for the domains are listed in the circles: negative cognitive biases (red), memory and working memory (yellow), reward-related processes (green), and sensory processing (purple).

ited significant reductions in brain-derived neurotrophic factor concentrations and gray matter volume in the dorsolateral and orbitofrontal cortex and hippocampus compared to controls [74]. While these findings are consistent with animal studies showing an association between social isolation and hippocampal neurogenesis [75], it is also conceivable that the expedition-related changes are a byproduct of sensory deprivation. Previous studies also observed that larger and more diverse social networks positively correlate with amygdala volume [76], but a recent study failed to replicate this association [77]. Along these lines, a rare patient with bilateral amygdala damage showed a normal size and complexity of her social network [78], indicating that an intact amygdala is not necessary to maintain social relationships or at least can be compensated for [79]. Several years after the first assessment of the social network, the woman with amygdala lesion developed severe treatment-resistant depression along with a reduction in the size of her social network, and she reported strong feelings of loneliness [80], demonstrating that the experience of loneliness may not require an intact amygdala either. However, recent large-scale brain morphology studies suggest that there are sex-dependent brain volume effects of loneliness, especially in the amygdala and the ventromedial prefrontal cortex (vmPFC) [81]. Smaller amygdala volumes were detected for lonely men, but not lonely women, and this pattern was reversed for the vmPFC volume. Thus, prospective longitudinal studies are required to monitor sex-specific morphological changes that accompany chronic loneliness. Sex and loneliness interactions are not restricted to brain structural effects. A recent large databank study found that lonely individuals display volume deviations and functional communication changes in the DMN, identifying the DMN as a key component of perceived social isolation [82]. Interestingly, this loneliness-related effect was more prominent in men than women.

Furthermore, individual differences in loneliness correlated with gray matter density in the left posterior superior temporal sulcus, and this association was mediated by social perception skills [83]. Interestingly, the correlation remained significant after controlling for trait anxiety and

social network size, thus providing further support for the notion that loneliness and social anxiety are characterized by distinct neural phenotypes [84] and for the dissociation of loneliness and social isolation. Importantly, loneliness has also been linked to altered neural processing in various neurocognitive domains (Fig. 1), including negative cognitive biases, sensory processing, executive functioning, reward-related processes, and memory.

Negative Cognitive Biases

It has been hypothesized that the maintenance of loneliness is fueled by negative cognitive biases which make positive social interactions less rewarding and may foster even more social withdrawal [17, 85]. Mechanistically, lonely individuals may be more likely to perceive social stimuli as threatening and to evaluate themselves and others more negatively [19]. Feelings of alienation may result from larger self-other dissimilarity of activation patterns in the medial prefrontal cortex [86]. Furthermore, loneliness is associated with reduced interpersonal trust and a preference for larger social distances from unfamiliar others, and this behavioral phenotype is paralleled by reduced trust-associated activity in the anterior insula. Importantly, blunted functional connectivity between the anterior insula and occipito-parietal regions predicts diminished affective and oxytocinergic responses to positive social interaction [87]. Given that the anterior insula plays a key role in self-awareness and interoceptive processing [88], we hypothesize that the negative cognitive biases in loneliness are mediated by an external attention focus due to reduced generation of, or sensitivity to, internal physiological signals in social situations [89]. Further supporting evidence for this notion comes from a study showing that insula responses to emotional faces mediate the association between alexithymia and subjective isolation stress [63]. Additionally, the DMN has been recently identified as a key system involved in loneliness through large-scale UK biobank studies. Increased functional connectivity of the DMN [82] and overall increased network integration between the DMN and the attentional and visual networks in lonely subjects [90] may reflect exaggerated rumination during rest [91]. Furthermore, it has been suggested that negative cognitive biases such as the expectation of more negative social interactions may be based on the association between loneliness and distinct divergences in the structural covariation of DMN and hippocampus subregions [92].

In addition, loneliness may affect synchronization during social interactions, such that lonely people may require stronger activation of their observation execution system including the inferior frontal gyrus (IFG) and the inferior parietal lobule for alignment to compensate for some deficiency in their synchronization ability [93]. Further studies are warranted to probe possible causal pathways of how disrupted interoceptive processes and impaired synchronization may lead to social withdrawal and the chronicity of loneliness.

Sensory Processing and Executive Functioning

Loneliness-induced hypervigilance can be observed in a shift of visual and auditory attention to negative or threatening stimuli. These changes in sensory processing could be induced by alterations in the dorsal and ventral attention networks [90, 94]. Furthermore, there appears to be a bidirectional relationship between tactile processing and loneliness. Touch deprivation during COVID-19-related restrictions has been linked to higher anxiety and greater loneliness [95], but loneliness also positively correlated with touch avoidance [96]. The excitatory transcranial direct current stimulation to the right IFG slowed responses to observed touch in lonely individuals [96], indicating that the IFG may contribute to the perpetuation of loneliness by enhancing the avoidance of positive social cues. Likewise, olfactory impairment can severely disrupt close relationships [97]. Loneliness is higher in participants who experienced childhood maltreatment, which correlates with amygdala hyperreactivity and hippocampal deactivation in response to social stress odors [98]. Whether and how loneliness may affect the sensory integration of multiple modalities is still elusive. In addition, it has been hypothesized that reduced functional connectivity of the right middle/superior frontal gyrus to the cingulo-opercular network during rest may reflect diminished executive functioning in loneliness [99], but evidence for an association between loneliness and impaired executive functioning across the life span is scarce.

Reward-Related Processes

The activation patterns evoked by acute social isolation in the ventral tegmental area are similar to the craving-related activation pattern observed after fasting [18]. By contrast, dissociable responses were evident in the striatum, with fasting enhancing responses to food cues in

the nucleus accumbens and social isolation increasing responses to social cues in the caudate nucleus. Cacioppo et al. [100] showed reduced ventral striatum (VS) activity in lonely individuals while viewing pleasant pictures with social connotation, but other studies found no significant correlation between loneliness and VS responses to pleasant social stimuli [101], nor between loneliness and striatal dopamine synthesis capacity in healthy controls or patients with autism spectrum disorder [102]. These contradictory findings may be reconciled by taking the familiarity of the social context into account. For instance, another functional magnetic resonance imaging study reported selectively increased VS responses to images of close others compared to strangers in lonely individuals, possibly reflecting fear of alienation or rejection [16].

Memory and Working Memory

In line with the above-mentioned association between loneliness and cognitive decline, several studies have reported loneliness-related declines in episodic, semantic, and working memory in older adults [103–105]. In patients with major depressive disorder, loneliness had no significant effect on working memory performance, but it was linked to increased functional connectivity between the dorsolateral prefrontal cortex and inferior parietal cortex, indicating that loneliness may be associated with altered neural regulatory functioning in self-referential processing [106]. Of note, a recent study found that loneliness may influence trauma memory in a sex-dependent manner. Specifically, lonely men, but not lonely women, exhibited more intrusive thoughts after experimental trauma and this phenotype was related to amygdala hyperreactivity during both fear conditioning and habituation processes, suggesting that the limbic system is a potential target for interventions that increase social connectedness [73]. Furthermore, the above-mentioned alterations in hippocampus-DMN covariation may reflect the neurobiological basis for an increased negative memory retrieval [92]. Interestingly, these alterations seem to have distinct links to genetic components of loneliness [92, 107].

Neurocognitive Mechanisms Underlying Loneliness-Related Vulnerability

The current lack of longitudinal studies probing the trajectories of loneliness-associated neural changes hamper conclusions about causal mechanisms. However, given the strong involvement of the DMN in loneliness, it is conceivable that DMN dysregulation also contributes to the detrimental health effects of loneliness. For instance, loneliness has consistently been associated with cognitive decline in patients with Alzheimer's disease [57, 58], and DMN dysregulation has not only been linked to Alzheimer pathology and cognitive decline [108, 109], but also to psychiatric disorders such as substance abuse [110], depression [91, 111], and post-traumatic stress disorder [112, 113]. Perceived social isolation could therefore influence different pathologies by changing the structural and functional integrity of the DMN.

A second possible mechanism mediating detrimental health effects of loneliness could be based on disrupted interoceptive processes. Loneliness has been linked with an "attentional switch" leading to a shift in the direction of heightened exteroceptive attention rather than interoceptive processes which may foster the negative cognitive bias in loneliness [89]. A perceptual insensitivity to the modulation of interoceptive signals has been observed across several common psychiatric disorders such as depression and anxiety disorder [114, 115]. This way, loneliness-dependent activity and connectivity changes in the anterior insula may reflect heightened subjective isolation stress and could convey increased vulnerability in lonely individuals to psychological disorders [63, 87].

Furthermore, amygdala hyperreactivity might be another mechanism underlying the elevated prevalence of psychiatric disorders in high-lonely individuals. Recently, we found amygdala hyperreactivity and increased intrusive thought formation after trauma exposure in high-lonely men [73]. Heightened amygdala reactivity predicts depressive [116] and post-traumatic stress disorder symptoms [117]. Furthermore, amygdala connectivity with the DMN is decreased in patients with major depressive disorder [118]. All of these hypothesized neurocognitive mechanisms might be possible targets for specific therapeutic interventions to reduce loneliness-related vulnerability, but rigorous randomized clinical trials are required to probe causal effects.

Therapeutic Interventions for Loneliness and Integration with Neurocognitive Mechanisms

Social interventions should be considered in new therapeutic concepts to effectively reduce feelings of loneliness. Several studies support the effectiveness of social interventions in a non-clinical environment [119–122]. Intervention types range from group-based physical

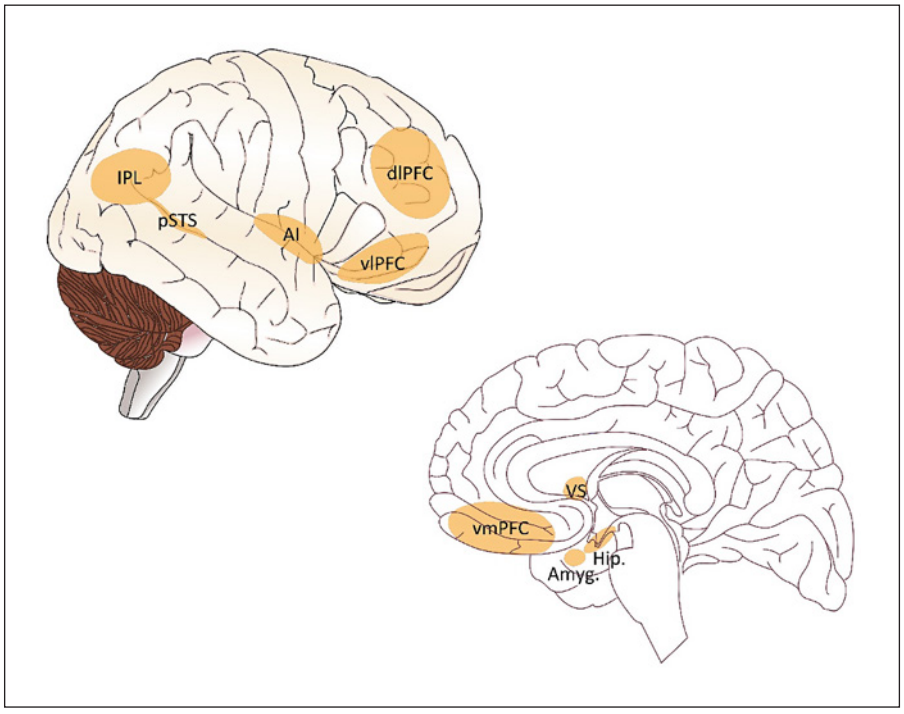

Fig. 2. Illustration of brain areas involved in loneliness. Chronic loneliness has been associated with functional and structural changes in various neural circuits of social and affective brain systems, including limbic regions such as the amygdala, hippocampus, and the anterior insula, as well as striatal, prefrontal, and temporal regions. Amyg., amygdala; dlPFC, dorsolateral prefrontal cortex; Hip., hippocampus; IPL, inferior parietal lobule; AI, anterior insula; VS, ventral striatum; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; pSTS, posterior superior temporal sulcus. Source of the brain template picture used to display the brain regions from https://scidraw.io/ (shared under the creative commons license CC-BY license).

activities [123–125], internet and app-based group interventions [126–128] to the use of robotic agents [129, 130]. In addition, a positive social climate and community programs can further prevent loneliness [131–133]. A recent meta-analysis showed that psychological interventions were more effective than measures to increase access to other people to improve the perceived quality of social connections [134]. For example, cognitive-behavioral therapies targeting maladaptive cognition can reduce loneliness levels and the elevated blood pressure associated with loneliness in older individuals [135, 136]. Furthermore, mindfulness training has been demonstrated to be effective in reducing loneliness and related pro-inflammatory gene expression [137–139]. Further studies have focused on designing and evaluating internet- or tele-delivered approaches that may facilitate more scalable and accessible interventions for chronic loneliness. A recent randomized controlled trial compared ICBT and internet-based interpersonal psychotherapy (IIPT) and demonstrated a significantly greater efficacy of ICBT than IIPT in reducing loneliness [2]. Similarly, a short-term tele-delivered intervention that aimed at facilitating social connectedness showed promising results in older adults by reducing feelings of loneliness and depression [140]. CBT and group therapy sessions also significantly increased social support and decreased depression scores after coronary heart disease [141]. Nevertheless, one-to-one peer support did not significantly reduce readmission rates in the year after discharge from inpatient psychiatric care [142], indicating that more specific interventions may be required. Overall, there is growing evidence that behavioral and psychological interventions targeting loneliness are an effective way to increase the feeling of social connectedness and additionally reduce harmful health effects. Despite increasing evidence demonstrating the efficacy of behavioral interventions for loneliness, the brain-based mechanisms mediating interventional effects have not been examined. Future prospective studies are needed to differentiate predisposing brain alterations that render individuals vulnerable to chronic loneliness from alterations as a consequence of prolonged loneliness and those that normalize during the course of successful treatment. Based on the notion of loneliness as biosocial pathogenesis, longitudinal studies are required to distinguish whether loneliness-related neural changes reflect damage as a direct consequence of excessive exposure to this stressor or adaptive processes which shape the brain in an experience-dependent plastic manner to cope with the negatively perceived social environment [36]. Similar approaches lead to a better understanding of the neural mechanisms in childhood maltreatment and should be adapted in future loneliness research [143].

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Moreover, a better understanding of the neurocognitive mechanisms mediating chronic loneliness opens up novel opportunities to enhance the efficacy of loneliness interventions by targeting the underlying brain circuits. Loneliness-related functional and structural brain changes are evident in various neural circuits of social and affective brain systems, including limbic regions such as the amygdala, hippocampus, and the anterior insula, as well as striatal, prefrontal, and temporal regions (Fig. 2). Alterations in the underlying brain circuits have been associated with detrimental effects of loneliness in various functional domains, which appear to be distinct from the consequences of depression [144] and social anxiety [84]. Therapy outcomes may be improved when interventions focus on multiple functional domains and the related neural targets. For instance, accumulating evidence from basic research and proof-of-concept studies suggests that targeting hormonal systems such as the oxytocin or vasopressin system may have the potential to facilitate social functioning in relevant domains in both healthy individuals and patients with mental disorders [145]. A single intranasal dose of oxytocin reduced aversive anticipation in high anxious individuals [146] and prevented sensitization towards angry faces [147] via reducing amygdala reactivity. Furthermore, oxytocin was found to enhance approach behavior towards positive social stimuli by modulating responsivity of the anterior insula [148, 149]. Both single-dose administrations of oxytocin and vasopressin may enhance the salience of social stimuli and decrease reactivity towards negative social feedback [150, 151]. Although neuropeptide treatment effects in these domains may vary as a function of dosage [152, 153], treatment expectation [154–156], and sex [157–159], the adjunct administration in combination with behavioral interventions may represent a promising venue to enhance the efficacy of loneliness interventions. Likewise, the endogenous oxytocin response to positive social interactions seems to be attenuated in high-lonely individuals [87], but repeated exposure to situations that have been found to induce the release of endogenous oxytocin such as massage, choir singing, or interpersonal synchronized behavior may reinstate normal neurohormonal responses [160–162].

Conclusion

Taken together, loneliness is a crucial and modifiable risk factor for physical and mental health. A better understanding of the neural underpinnings of social (dis)connectedness can help boost the efficiency of loneliness interventions not only in healthy participants but also in patients with mental disorders.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.M., X.L., R.H., B.B and D.S. all made substantial contributions to the conception of this paper. M.M. and D.S. drafted this paper, and X.L. and B.B. contributed critical revisions for intellectual content. All of the authors had final approval of all of the submitted versions, and all are in agreement to be accountable for all aspects of this work. A preprint of the manuscript has been posted on the Psyarxiv repository (DOI: 10.31234/osf.io/r4f9e).

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4. Discussion

This thesis investigated the mechanistic connection between loneliness and psychosocial stress and their implications for psychological well-being. The results of the first study showed that subjects with high alexithymia experienced higher levels of psychosocial stress during transition phases, a finding which is consistent with previous studies (Kerr et al., 2004). In extension to the stress-alexithymia hypothesis, the results revealed that this connection is mediated by feelings of loneliness. More specifically, subjects struggling with characterizing and expressing their emotions, experience more loneliness and thus more psychosocial stress. Therefore, as hypothesized in RQ 1, loneliness indeed influenced the interplay between alexithymia and stress. Additionally, reduced insula reactivity to emotional stimuli mediated this harmful association of psychosocial stress and alexithymia via loneliness. Interestingly, the insula is seen as an interoceptive processing hub and has been linked to social interest and interpersonal trust decisions, further strengthening the notion that detrimental loneliness effects might be influenced by altered insula reactivity (Hannestad et al., 2012; Lieberz et al., 2021; Zaki et al., 2012).

The second study revealed that romantic relationships and living with others were effective buffers for feelings of loneliness during the COVID-19 lockdown, as assumed in RQ 2. In addition, being in a romantic relationship, in contrast to living with others, even altered neuroendocrine stress response shown by reduced diurnal cortisol levels. This study provides further evidence for the social buffering hypothesis and the interplay of loneliness and psychosocial stress during periods of prolonged social isolation. As such, the study revealed that women exhibited higher loneliness levels than men and similar results were obtained in other studies during COVID-19, indicating sex differences in feelings of loneliness (Wickens et al., 2021).

Given the influence of sex on amygdala volume, loneliness, and trauma, the third study tried to expand the knowledge on the roles of sex and loneliness in neural fear processing, thereby probing potential neural pathways conveying vulnerability for increased intrusive thought formation. The results demonstrated that, even though loneliness did not alter acute stress response to traumatizing film footage, there were sex- and loneliness-dependent changes in intrusive thought formation, showing that lonely men exhibited higher levels of intrusions than lonely women. As supposed in RQ 3, perceived social isolation was linked to reduced amygdala habituation to fear signals and amygdala

hyperreactivity during fear conditioning, indicating that loneliness might act as a potential risk factor for PTSD in lonely men.

This thesis identified the insula and amygdala as potential brain regions involved in both psychosocial stress and loneliness. As described in the review article (study 4), previous studies also linked insula activity to social exclusion and approach behavior (Mwilambwe-Tshilobo et al., 2021; Yao et al., 2018). In addition, loneliness was associated with sex-dependent amygdala volume changes (Kiesow et al., 2020), further strengthening the notion that the limbic system is vigorously involved in feelings of loneliness. Considering that in contrast to study 1, study 2 and study 3 found sex-related differences in loneliness, perceived social isolation might be a domain-specific moderator variable and thence should be addressed in further research.

All in all, the current thesis provides novel insights into the dynamics of loneliness and psychosocial stress perhaps illustrating a reciprocal relationship between both constructs. Our findings indicate that loneliness acts as a crucial risk factor for increased psychosocial stress and additionally suggest that the consequences of stressful events like trauma exposure depend on feelings of loneliness. The observed changes in the amygdala and insula reactivity might connect perceived social isolation and psychosocial stress mechanistically, probably identifying a neural pathway by which loneliness conveys its deleterious health effects.

4.1. Limitations and outlook

Higher allostatic load due to increased loneliness and stress, is associated with diverse mental health problems and the current thesis indicates that the limbic system might play a crucial role in connecting psychosocial stress and feelings of loneliness. Nevertheless, this thesis tested only healthy participants hampering the transferability. More research is needed to test how loneliness interacts with stress and how this interplay affects neural pathways in patient populations. Despite the altered insula reactivity to emotional stimuli (study 1) and a possible amygdala hyperreactivity (study 3) covered in this thesis, another neural alteration potentially conveying deleterious health effects is the DMN, which was recently associated with loneliness-related connectivity changes (Spreng et al., 2020). DMN dysfunctions were linked to various psychological diseases, such as depression and PTSD (Akiki et al., 2018; Zhou et al., 2020) and acute stress seems to increase DMN

activity (van Oort et al., 2017). Therefore, an interconnection between DMN abnormalities, loneliness, and psychopathology is conceivable and should be studied more thoroughly.
The conducted studies showed that loneliness confers vulnerability to mental health problems and increased psychosocial stress, hence loneliness should be addressed in new therapeutic guidelines. Social interventions provided promising results in reducing feelings of loneliness in a non-clinical environment (Williams et al., 2022) and psychological interventions targeting loneliness even reduced physiological maladies like high blood pressure and inflammatory gene expression (Creswell et al., 2012; Theeke et al., 2016). In addition, a recent study demonstrated that internet-based cognitive behavior therapy is more effective in reducing feelings of loneliness than internet-based interpersonal psychotherapy (Käll et al., 2021). Recapitulatory, there is growing evidence that increasing social connectedness via loneliness interventions is able to improve therapeutic health outcomes by reducing the allostatic load. Nevertheless, data on neurocognitive mechanisms underlying these positive effects are scarce. Prospective studies should focus on neuronal changes accompanying clinical interventions. Furthermore, identifying neural mechanisms of loneliness could help to classify individuals with a heightened vulnerability to feelings of loneliness. Looking at loneliness in light of biosocial pathogenesis, longitudinal studies are desperately needed to distinguish if neuronal changes related to loneliness might either be an adaptive coping process or a detrimental consequence of chronic stress exposure (Horwitz et al., 2022). A deeper insight into the neurocognitive interplay between loneliness and stress could open new avenues for therapeutic interventions. In the future, neurofeedback training or transcranial magnetic stimulation targeting loneliness-affected brain regions could support therapeutic approaches.

4.2. Conclusion

The provided studies broadened the knowledge of the closely intertwined phenotypes of loneliness, psychosocial stress and their neural underpinnings. The study outcomes might indicate a reciprocal relationship between psychosocial stress and perceived social isolation, such that loneliness constitutes a risk factor for increased stress but also influences the reaction to stressful and even traumatic events. This relationship could be connected with altered reactivity in the limbic system (e.g., amygdala, insula). The current

results highlight the importance of loneliness for mental health problems like trauma and alexithymia. Therapeutic interventions should consider the relevance of the social environment to reduce stress levels and symptom load. Deepening the understanding of the neural pathways of loneliness might help to tailor neurobiologically informed interventions targeting loneliness and reducing stress.

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6. Publications

Number of publications: 5
Average impact factor [IF]: 11.65

Wittenberg MA, **Morr M**, Schnitzler A, Lange J. 10 Hz tACS over somatosensory cortex does not modulate supra-threshold tactile temporal discrimination in humans. Front Neurosci 2019; 13: 311 [IF: 5.15]; https://doi.org/10.3389/fnins.2019.00311

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Hopf D, Schneider E, Aguilar-Raab C, Scheele D, **Morr M**, Klein T, Ditzen B, Eckstein M. Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality. Sci Rep 2022; 12(1): 15076 [IF: 4.99]; https://doi.org/10.1038/s41598-022-19224-2

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